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BIOLOGICAL IMPORTANCE OF THE PYRIMIDINE NUCLEUS IN RECENT YEARS: A COMPREHENSIVE REVIEW

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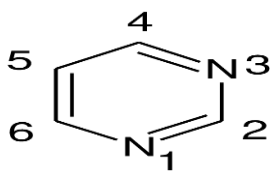
Abstract
Pyrimidine nucleus showed clinical and biological applications. Pyrimidine scaffold has been found in many of the important synthetic drug molecules which gave a valuable idea for treatment and binds with high affinity to the multiple receptors helpful in developing new useful derivatives. Pyrimidine derivative possess various types of biological activities i.e., antiviral, anti-inflammatory, anti-cancer, anti-HIV, antioxidant, antimicrobial, anti-tubercular activities, etc. This review created interest among researchers to synthesize a variety of pyrimidine derivatives. Literature data revealed that thepyrimidine derivatives have exhibited diverse biological activities and also have immeasurable potential to be explored for newer therapeutic possibilities.

Keywords: pyrimidine, anti-inflammatory, anti-cancer, anti-malarial, antioxidant, anti-tubercular, antimicrobial activities.

Introduction

Heterocyclic Compounds, pyrimidine in particular have recently seen increased interests in researchers due to their therapeutic benefits and also shows many biological activities[I]. After Scheele isolated uric acid in 1776, fused pyrimidine chemistry started. Pyrimidine is a heterocyclic aromatic organic compound containing two nitrogen atoms at positions 1 and 3 of the six- member ring similar to pyridine.

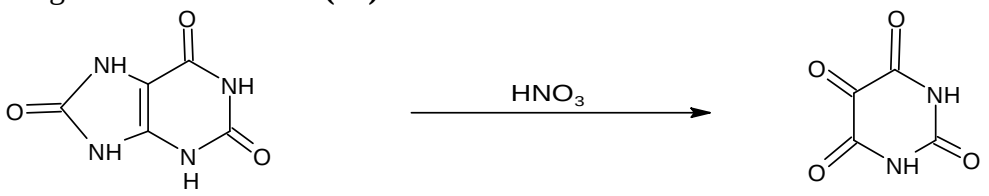


1a

The name of the pyrimidine was first applied by Pinner from the combination of two words pyridine and amidine. Pyrimidines (1,3-diazines) and their fused analogues form a large group of heterocyclic compounds. Pyrimidine which is an integral part of DNA and RNA imparts diverse pharmacological properties[II-III]. The pyrimidine have been isolated from the nucleic acid hydrolyses and much weaker base than pyridine and soluble in water with its more uses coming into light, the area of different pathways of synthesis of the pyrimidine derivatives have gained considerable attention. The classical Beginelle reaction one-pot synthesis has provided a base to develop newer 'greener' versions[IV] of the pyrimidine derivatives. Pyrazole and pyrimidine are very important moieties in heterocyclic chemistry. There are many commercial drugs available in the market having these frameworks[V]. Recently, many efforts have been made to explore the biological importance of pyrimidine derivatives[VI-VII] Pyrimidines and their related fused heterocyclic derivatives possess antibacterial[VIII], antifungal[IX], antiviral[X], anti-influenza[XI], antioxidant[XII], anti-inflammatory[XIII], antimalarial[XIV], antiproliferative[XV], and antitumor[XVI] activities[XVII-XVIII] . In addition, pyrido[2,3-*d*]pyrimidines exhibit antimicrobial, antifungal, and anti-inflammatory activities[XIX-XXI] while thieno[2,3-*d*]pyrimidines exhibit antiproliferative and anti-inflammatory activities[XXII-XXIV]. Moreover, [1,2,4]riazolopyrimidine derivatives exhibit antimicrobial, antifungal, antioxidant, anti-inflammatory, antimalarial, analgesic, and antitumor activities [XXV-XXX].

Few methods of synthesis of pyrimidine derivatives:

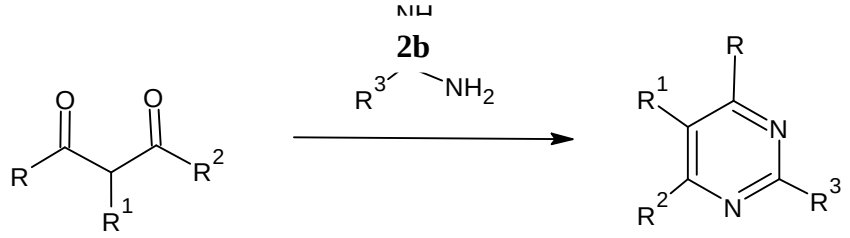
In 1818, Brugnatelli synthesized the first pyrimidine derivative, alloxan**(1c)** , by nitric acid oxidative degradation of uric acid**(1b)** [XXXI]



7,9-dihydro-1*H*-purine-2,6,8(3*H*)-trione — alloxon

1b **1c**

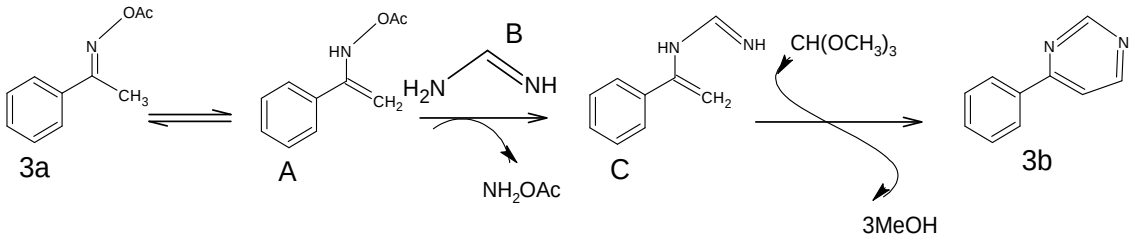
Pyrimidine derivatives are typically accessed by the acid or base catalyzed condensation of 1,3-dicarbonyl compounds**(2a)** with amidines**(2b)** (Pinner pyrimidine synthesis)



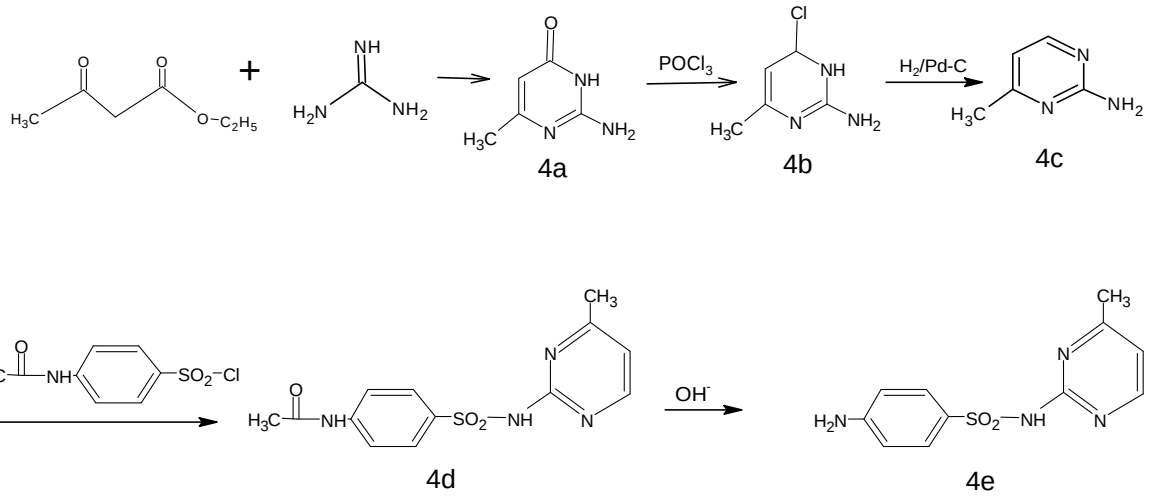
2a

R^2,R^3= H, Ph, CH_3

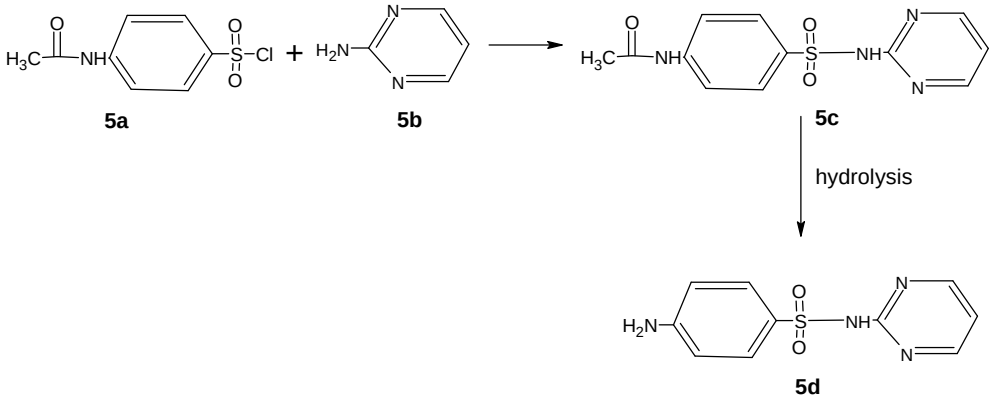
In another method suggested by Atul Upare and Teledor D et. al[XXXII-XXXIII] the reaction is initiated by the formation of enamine intermediate A, a tautomer of oxime acetate **3a**. Next, intermediate C is formed by the condensation reaction of A with B (in situ generated formamidine) via the expulsion of NH_2OAc. Finally, intermediate C reacts to produce the corresponding pyrimidine **3b**



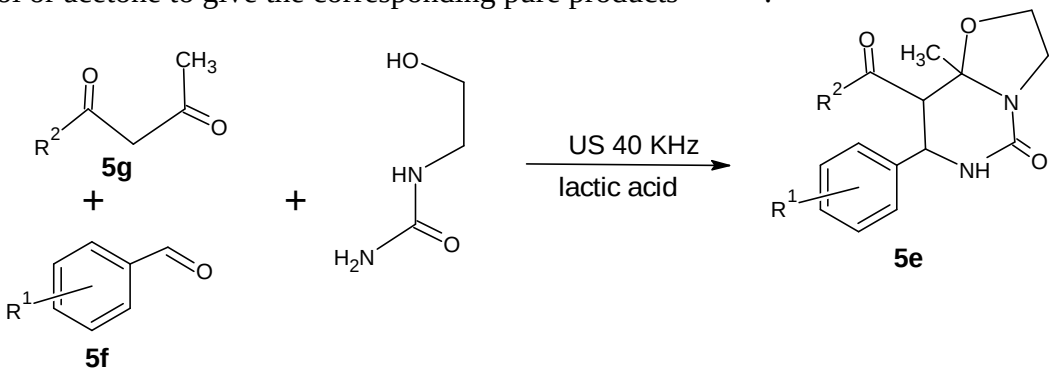
Robin et.al[XXXIV] Sulfamerazine, N1-(4-methyl-2-pyrimidinyl)sulfanilamide, is obtained by reacting 4-acetylaminoben-zenesulfonyl chloride with 2-amino-4-methylpyrimidine, which is in turn synthesized by the traditional scheme of synthesizing derivatives of pyrimidine. Northey[xxxv], Sprague[xxxvi] and Vardanya[xxxvii] Acetoacetic ester is condensed with guanidine to give 4-methyl-2-aminopyrimidin-6-one**(4a)**. Reacting this with phosphorous oxychloride gives 4-methyl-2-amino-6-chloropyrimidine **(4b)**. The chlorine atom at C6 of the pyrimidine ring is then removed by reduction with hydrogen using a palladium on carbon catalyst. The resulting 4-methyl-2-aminopyrimi- dine**(4c)** is then reacted with 4-acetylaminobenzenesulfonyl chloride**(4d**) to make an acetanilide derivative , the subsequent hydrolysis of which with base leads to the formation of the desired sulfamerazine **(4e)**



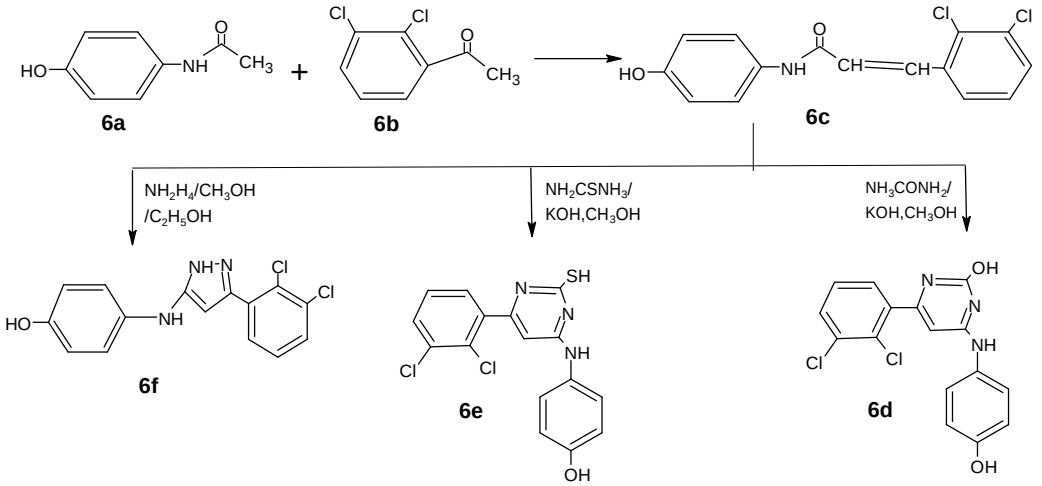
The synthesis of sulfadiazine has been described by Roblin[XXXVIII] and Northey [XXXIX]. The synthetic reactions consist of condensing 2-aminopyrimidine**(5b)** with p-acetamido-benzenesulfonyl chloride**(5a)**, followed by hydrolysis of the - N4-acetyl group with sodium hydroxide[XL] .



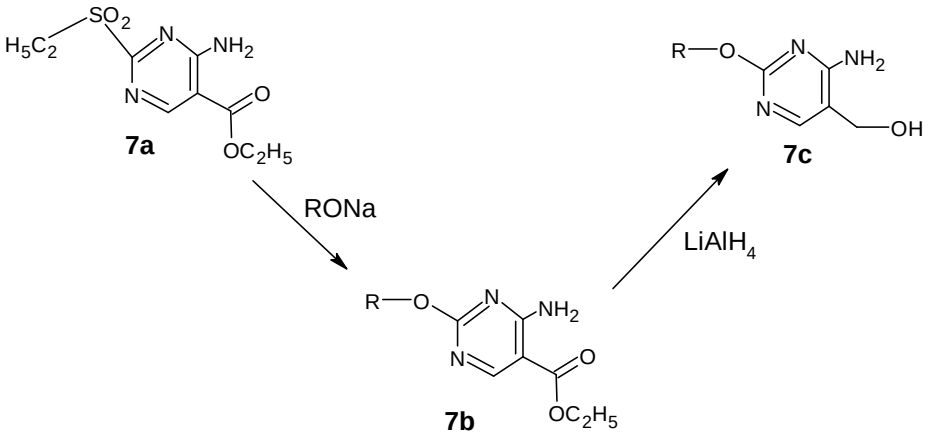
In a 'solvent-less' mechano-chemical method, mixture of acetoacetate (3 mmol), aromatic aldehyde (3 mmol), amine (3 mmol), and NS-5 (0.4 mol %) in a milling jar (80 mL) is milled with 20 milling balls (5 mm) at 600 rpm for 40 min at room temperature under argon. The product is re-crystallized from an acetone/water mixture[XLI] or the synthesis of compound **5e** in lactic acid, 1,3- dicarbonyl com-pound (5g) (1 mmol), corresponding aldehyde **(5f)** (1 mmol), 1-(2-hydroxy ethyl) urea (1.2 mmol) are added in a conical flask under ultrasonic irradiation (40 kHz, 500 W) at 65–80℃ for 0.5 h until the reaction is accomplished. The reaction progress is monitored by TLC. The reaction mixture is poured into a large beaker with ice water, a large amount of solids are precipitated, and allowed to stand for a while. After suction filtration, the filter cake is obtained, washed with water, and recrystallized from ethanol or acetone to give the corresponding pure products[XLI-XLII].



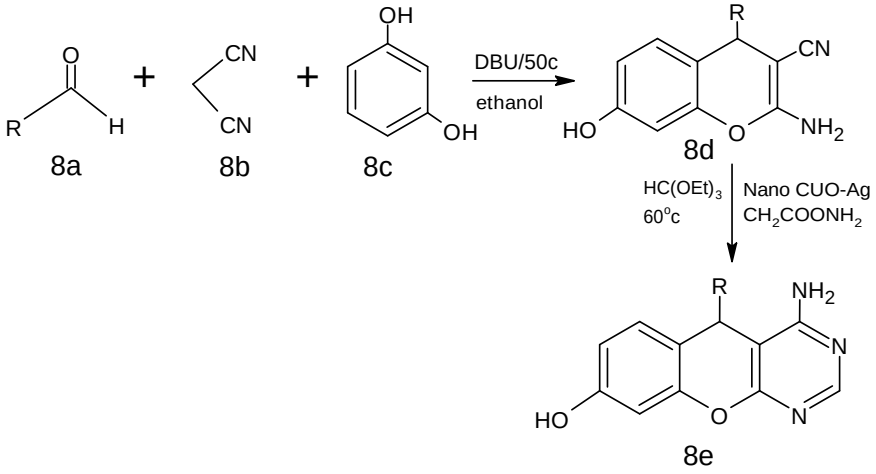
Treatment of paracetamol **(6a)** with 2,3-di chlorobenzaldehyde **(6b)** in solution of KOH at 298k afford chalcones **(6c).** Reaction of chalcones **(6c)** with urea and potassium hydroxide in methyl alcohol yield the corresponding **(6d)** ,Also treatment of chalcone (**6c**) with Thiourea and KOH in methyl alcohol give compound **(6e),** treatment of chalcone **(6c)** and hydrazine monohydrate in AcOH provide the Corresponding **(6f),** the product recrystallized with ethanol[XLIII].



4-Amino- 5 - carbethoxy - 2 - (ethylsulfony1)pyrimi- dine8 **(7a)**, when treated with sodium methoxide, gave 4-amino-4-carbethoxy-2-methoxypyrimidine (7b,. R = CH_3).9 Reduction of **7b** with lithium aluminum hydride in anhydrous ether or tetra- hydrofuran gave a 67% yield of 4-amino-5-hydroxy- methyl-2-methoxypyrimidine(Bacimerthin) (**7c**. R = CH)[XLIV]



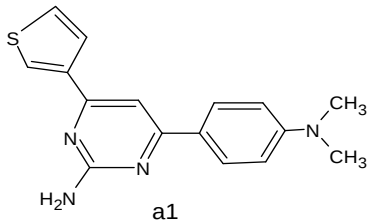
Synthesis of **(8e)** proceed via two-step ,in the synthesis of **(8e)** through the conventional method involves substituted aldehydes **(8a)** to be treated with, malanonitrile **(8b),** and 1, 3 dihydroxy benzene **(8c)** afford the corresponding pyran derivatives **(8d)**. Cyclization of pyrane derivatives **(8d)** by using nano catalyst provides **(8e)**. This is a green method and is highly efficient, also the reaction occurs without catalysts by using reflux for 8 hours[XLV]



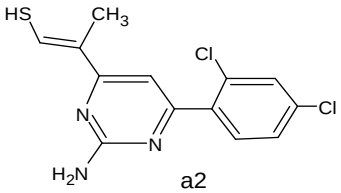
Biological Activities of pyrimidine derivatives:

Antimicrobial activity

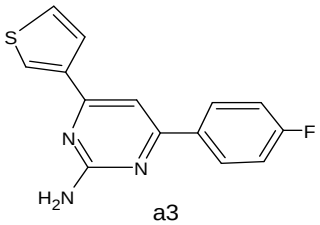
The growing health problems demands for a search and synthesis of a new class of antimicrobial molecules which are effective against pathogenic microorganisms. Despite advances in antibacterial and antifungal therapies, many problems remain to be solved for most antimicrobial drugs available. The extensive use of antibiotics has led to the appearance of multidrug resistant microbial pathogens which necessitated the search for new chemical entities for treatment of microbial infections. Anupama et al. synthesized a series of 2,4,6-trisubstituted pyrimidines by reacting chalcone with guanidine hydrochloride. All the synthesized derivatives were confirmed by physicochemical properties and spectral data(IR, NMR and elemental analyses) and screened their in-vitro antimicrobial activity against bacterial and fungal strains by cup plate method using Mueller–Hinton agar medium. Among the derivatives tested, compounds, **a1, a2** and **a3** exhibited promising activity against microbial strains (*B. pumilis, B. subtilis, E. coli, P. vulgaris. A. niger* and *P. crysogenium*) and showed activity comparable with standard drugs. Structure activity relationship (SAR) studies indicated that compounds, **a1, a2** and **a3** having dimethylamino, dichlorophenyl and fluorine substituent on the phenyl ring at 4th position respectively exhibited better antimicrobial activity[XLVI].



a1

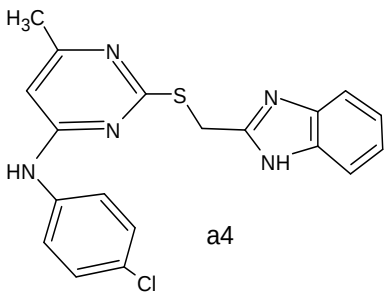


a2

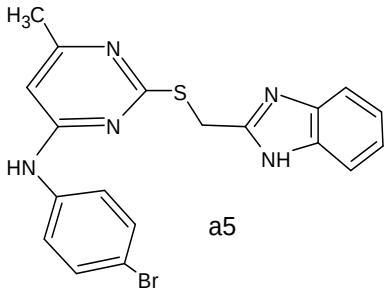


a3

Chen et al. synthesized a novel series of 4-substituted-2-{[(1*H*-benzo[*d*]imidazol-2-yl) methyl]thio}-6-methylpyrimidines from pyrimidine–benzimidazole combination. All the synthesized derivatives were fully characterized by 1H-NMR, 13C-NMR and HRMS study and screened its in vitro antimicrobial activity against Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*), Gram-negative bacteria (*Escherichia coli*, *Stenotrophomonas maltophilia*) and fungi (*Candida albicans*). The minimum inhibitory concentration (MIC) of the target compounds was determined by broth microdilution method and compared to two commercial antibiotics (levofloxacin and fluconazole). Among the entire synthesized derivatives, compounds, **a4** and **a5** were found to be the most active antimicrobial agents. Structure activity relationship showed that aromatic amines at pyrimidine ring are beneficial for the antimicrobial activity. Besides, the aniline containing *para*-substituted groups (especially Cl and Br) is more beneficial for the activity[XLVII].

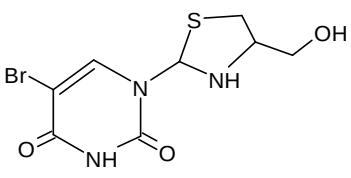


a4

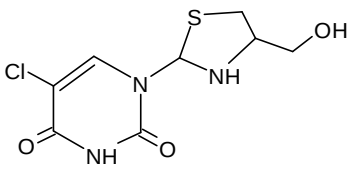


a5

Sriharsha et al. developed a new series of novel 1,3-thiazolidine pyrimidine derivatives and carried out its antibacterial activity against 14 bacterial strains i.e. *Citrobacter* sp., *Escherichia coli*, *Klebsiella* sp., *Proteus mirabilis, Pseudomonas aeruginosa, S. parathyphi A, S. parathyphi B, Salmonella typhi, S. typhimurium, Shigellaboydii, Shigella flexneri, Shigella sonnei, Staphylococcus aureus* and *Streptococcus faecalis.* All compounds with free NH group in the pyrimidine moiety showed significant biological activity against all the standard strains used and in that compounds **a6** and **a7** showed promising activity against 14 human pathogens tested and compared with the ciprofloxacin and bacitracin used as standard drugs[XLVIII.]

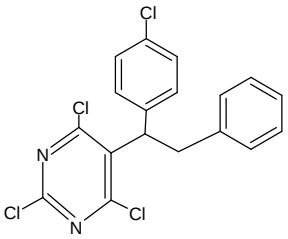


a6

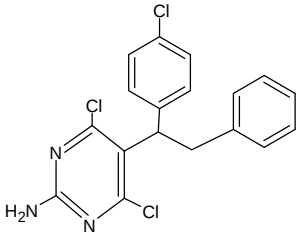


a7

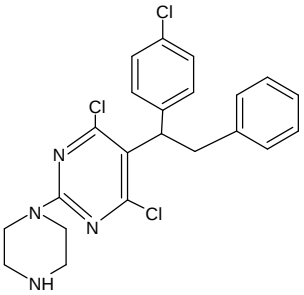
Fellahil et al. synthesized a new series of 5-(1,2-diarylethyl)-2,4,6-trichloro pyrimidines and 2-amino- and 2-(1-piperazinyl)-5-(1,2-diarylethyl)-4,6-dichloro pyrimidines via organozinc reagents and demonstrated its antibacterial activity against human bacterial flora. Biological tests showed that 5-[1-(4-chlorophenyl)-2-phenylethyl]- 2,4,6-trichloro pyrimidine derivatives i.e. compounds **a8** and **a9** were found to be most active against wide range of bacterial flora of the axilla and foot, while 2-(1-piperazinyl)-4,6-dichloro pyrimidine derivatives **a10** and **a11** displayed a great selectivity against *Corynebacterium xerosis* and *Arcanobacterium haemolyticum* of the human axilla[XLIX].



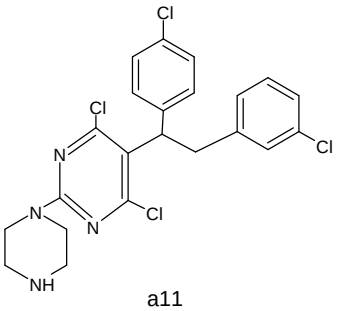
a8



a9

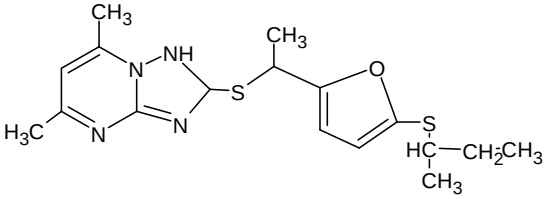


a10

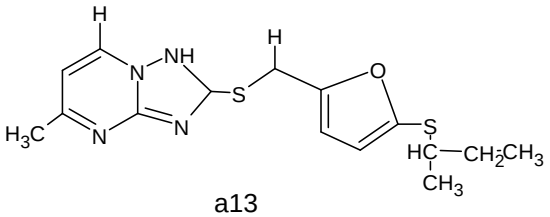


a11

A new series of 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives bearing 1,3,4-oxadiazole moieties was designed and synthesized by Chen et al. The molecular structures of all new compounds were characterized by spectral means (^{1}H-NMR, Mass and elemental analyses) and evaluated their in vitro antifungal activity against *Rhizoctonia solani*. In this series, compounds, **a12** and **a13** displayed the highest antifungal activity against *Rhizoctonia solani* with EC50 = 3.34 µg/ml and EC50 = 6.57 µg/ml values respectively than the carbendazim (EC50 = 7.62 µg/ml) due to presence of the *sec*-butyl group[L].

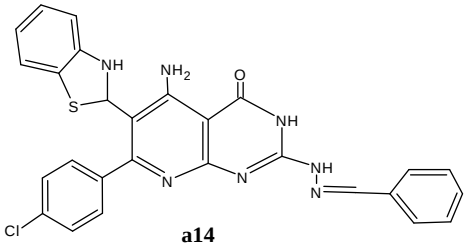


a12

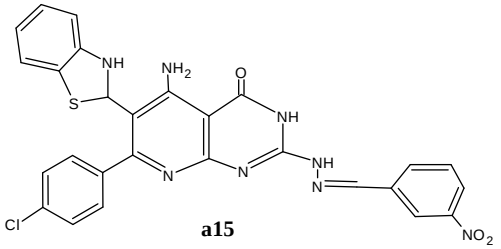


a13

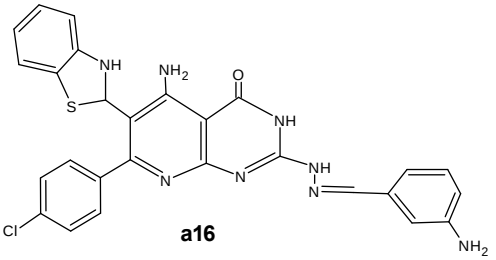
A new library of 5-amino-6-(benzo[*d*]thiazol-2-yl)-2-(2-(substituted benzylidene) hydrazinyl)-7-(4-chlorophenyl) pyrido[2,3-*d*]pyrimidin-4(3*H*)-one derivatives was synthesized by Maddila et al. and evaluated its antibacterial activity against *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Streptococcus pyogenes* and antifungal activity against *Aspergillus flavus, Aspergillus fumigatus, Candida albicans, Penicillium marneffei* and *Mucor* by the twofold serial dilution method. Compounds, **a14, a15** and **a16** showed excellent antibacterial and antifungal activity than the standard drugs ciprofloxacin and clotrimazole respectively[LI].



a14



a15

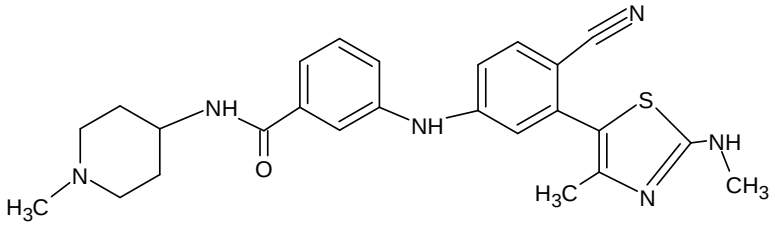


a16

Anticancer activity

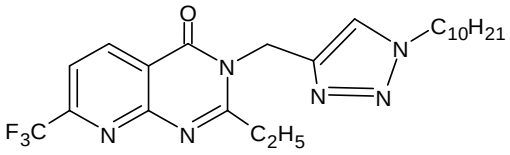
Chemotherapy is the mainstay for cancer treatment, the use of available chemotherapeutics is often limited due to undesirable side effects. It is important to identify new molecules and new targets for the treatment of cancer. Pyrimidines comprise important interesting group of antibacterial drugs, which have made a major impact on the field of antibacterial chemotherapy particularly in the past few years.

Shao et al. synthesized a new derivatives of 2,4,5-trisubstituted pyrimidine CDK inhibitors as potential antitumour agents. The synthesized 2,4,5-trisubstituted pyrimidine derivatives were evaluated for their antitumour activity against a panel of cancer cell lines including colorectal, breast, lung, ovarian, cervical and pancreatic cancer cells. Among the synthesized derivatives, compound **a17**, possessing appreciable selectivity for CDK9 over other CDKs, is capable of activating caspase 3, reducing the level of Mcl-1 anti-apoptotic protein and inducing cancer cell apoptosis[LII].

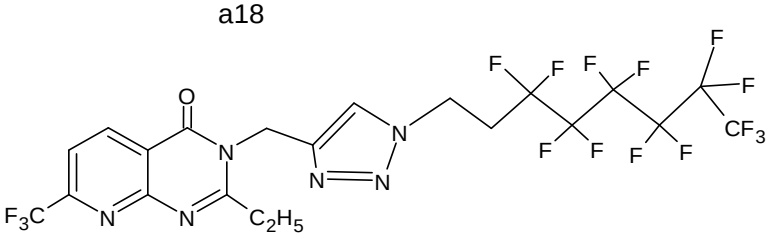


a17

Kumar et al. developed a new library of triazole/isoxazole functionalized 7-(trifluoromethyl)pyrido[2,3-*d*] pyrimidine derivatives and screened their anticancer activity against four human cancer cell lines using nocodazole as standard. Compounds **a18** and **a19** showed highest activity against PANC-1 (pancreatic cancer) and A549 (lung cancer) cell lines respectively[LIII].

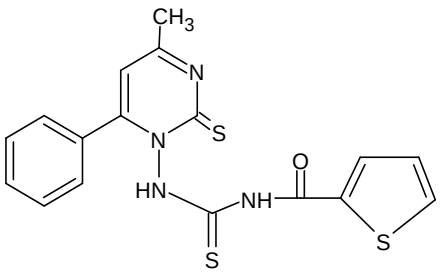


a18

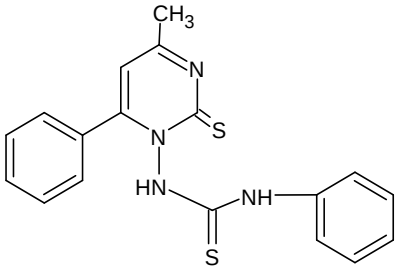


a19

Al-Issa, developed a new series of fused pyrimidines and related heterocycles and evaluated its in vitro antitumor activity against human liver cancer cell line (HEPG2). Structures of all synthesized compounds were supported by spectral and elemental analyses. Among the synthesized compounds, compounds **a20** and **a21** showed significant in vitro antitumor activity (IC50, 17.4,23.6 μg/ml)[LIV].

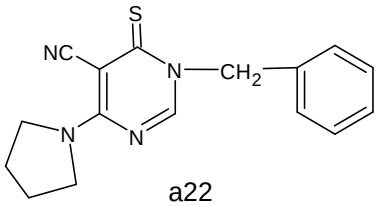


a20



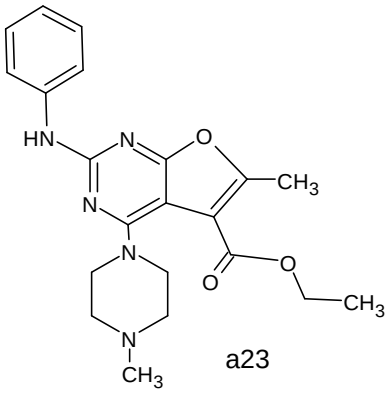
a21

Cocco et al. synthesized a new class of 6-thioxopyrimidinederivatives and its molecular structures were confirmed by IR, NMR and elemental analyses study. The synthesized derivatives were evaluated their in vitro anticancer potential against multiple panels of 60 human cancer cell lines by Sulforhodamine B assay. All synthesized 6-thioxopyrimidine derivatives exhibited good anticancer potential, especially, compound **a22** showed the best cytotoxicity[LV].



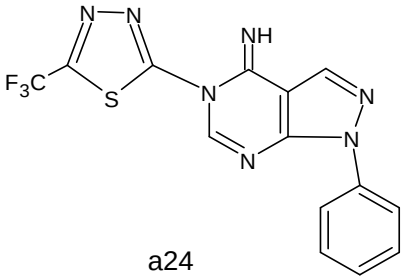
a22

Hu et al. developed a new library of 2,4-diaminofuro[2,3-*d*]pyrimidine and carried out its in vitro anticancer activity against A459 and SPC-A-1 cancer cell lines. Their structures were confirmed by 1H-NMR, EI-Ms, IR and elemental analysis. Among them, compound **a23**: ethyl-6-methyl-4-(4-methylpiperazin-1-yl)- 2-(phenylamino)furo[2,3-*d*] pyrimidine-5-carboxylate was found to be most anticancer one against lung cancer cell line (A459 with IC50 0.8 μM)[LVI].

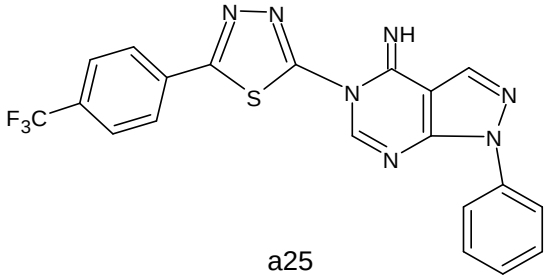


a23

Song et al. synthesized a new library of fluorinated pyrazolo[3,4-*d*]pyrimidine derivatives by microwave (MW) irradiation method and evaluated its in vitro antitumor potential against human leukaemia (HL-60) cancer cell line by MTT assay. The preliminary results demonstrated that some of compounds exhibited potent antitumor inhibitory potential than doxorubicin (standard drug), especially compounds, **a24** and **a25** exhibited higher antitumor activity due to presence of CF group in its molecule structure[LVII].

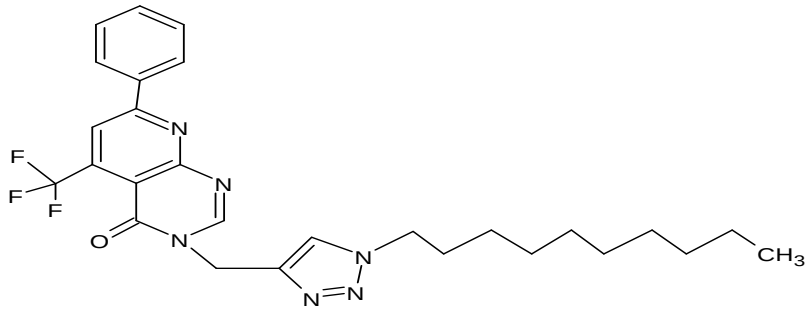


a24

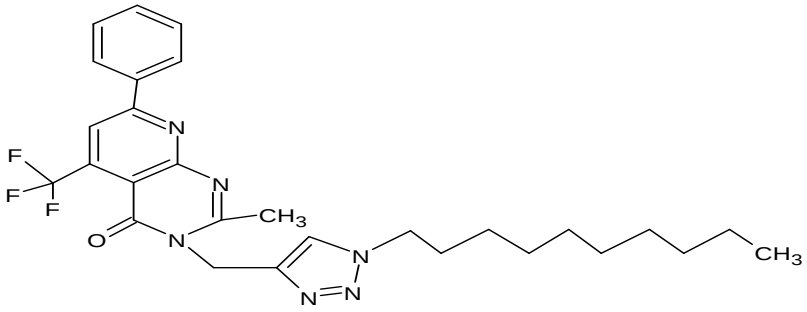


a25

Kurumurthy et al. prepared a novel class of alkyltriazole tagged pyrido[2,3-*d*] pyrimidine derivatives and its molecular structure were confirmed by IR, NMR, Mass and elemental analyses. The synthesized derivatives were evaluated for their in vitro anticancer activity against three cancer cell lines i.e. U937 (human leukemic monocytic lymphoma), THP-1 (human acute monocytic leukemia) and Colo205 (human colorectal cancer) using MTT assay. Among the synthesized molecules, compounds **a26** and **a27** exhibited better anticancer activity than the standard etoposide[LVIII]

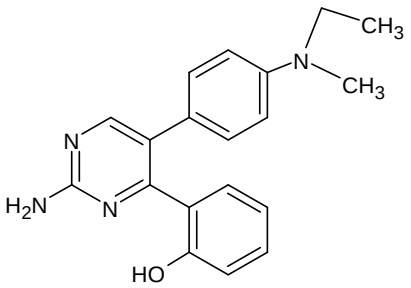


a26



a27

2,4,5-Substituted pyrimidine molecules were prepared and evaluated for their anticancer activity against different human cancer cell lines (A549, Calu-3, H460, SK-BR3, SGC-7901 and HT29) by Xie et al[LIX]. Among the synthesized molecules, compounds **a28** showed good inhibition of several different human cancer cell lines with IC50values from 0.024 to 0.55 μM[LIX].



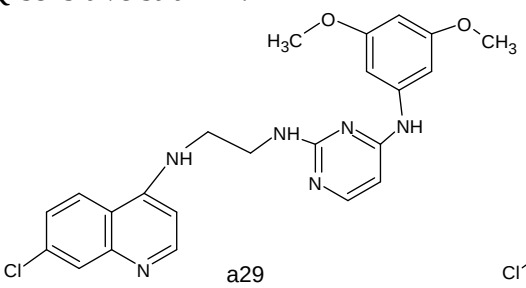
a28

Antimalarial activity

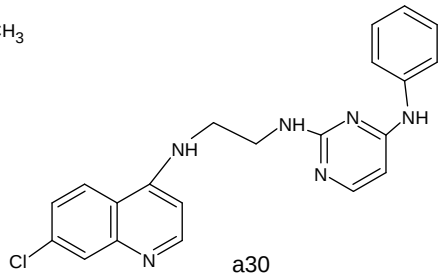
Malaria is the most serious and widespread parasitic disease because of its prevalence, virulence and drug resistance, having an overwhelming impact on public health in developing regions of the world. *Plasmodium falciparum* is the main cause of severe clinical malaria and death. Endemic mapping indicates that *P. falciparum* and *P. vivax* account for 95% of the malarial infections. According to a WHO report, malaria accounted for 207 million cases and an estimated 627,000 deaths worldwidein 2013[LX].

Kumar et al. synthesized a new series of 4-aminoquinoline- pyrimidine hybrids and evaluated its antimalarial potential. Several compounds showed promising in vitro antimalarial activity against both CQ sensitive and CQ-resistant strains with high selectivity index. The in vitro evaluation of these hybrids against D6 and W2 strains of *P. falciparum* depicted the antimalarial activity in the nanomolar range. Also, these hybrids exhibited high selectivity indices and low toxicity against the tested cell lines. Compounds (**a29, a30** and **a31)** exhibited very potent antimalarial activity with IC50 = 0.033, 0.019 and 0.028 μM

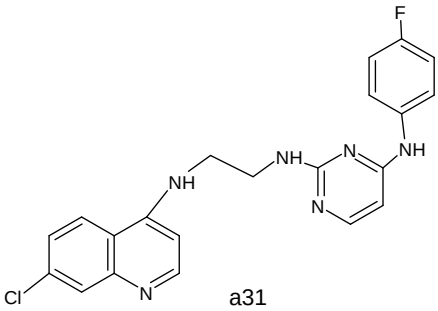
respectively which were comparable to the standard drug chloroquine (IC50 = 0.035 μM) against CQ-sensitive strain[LX].



a29

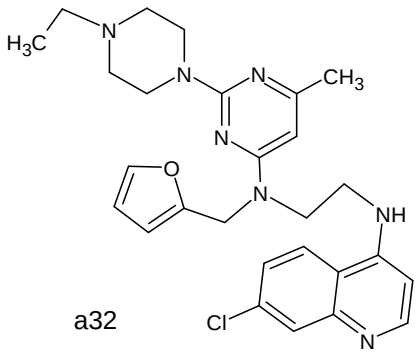


a30



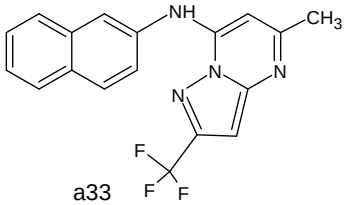
a31

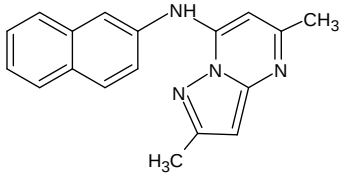
Maurya et al. developed a new series of novel *N*-substituted 4-aminoquinoline-pyrimidine hybrids via simple and economic route and evaluated its antimalarial activity. Most compounds showed potent antimalarial activity against both CQ-sensitive and CQ-resistant strains with high selectivity index. All the compounds were found to be non-toxic to the mammalian cell lines. The most active compound **a32** was analyzed for heme binding activity using UV spectrophotometer. Compound **a32** was found to interact with heme and a complex formation between compound **a32** and heme in a 1:1 stoichiometry ratio was determined using job plots. The interaction of these hybrids was also investigated by the moleculardocking studies in the binding site of wild type Pf-DHFRTS and quadruple mutant Pf-DHFR-TS [LXI].

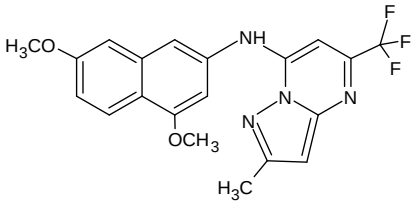


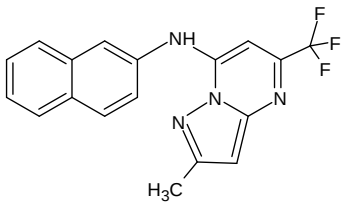
a32

Azeredo et al. synthesized a new series of 7-aryl aminopyrazolo[1,5-*a*]pyrimidine derivatives with different combinations of substituent's at positions 2-,5- and 7- of the pyrazolo[1,5-*a*]pyrimidine ring. The compounds were tested against *Plasmodium falciparum*, as antimalarials in mice with *P. berghei* and as inhibitors of *Pf*DHODH. From this series, compounds, **a33, a34, a35** and **a36** were found to be the most active ones[LXII].

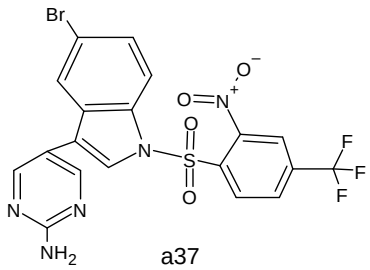

a33

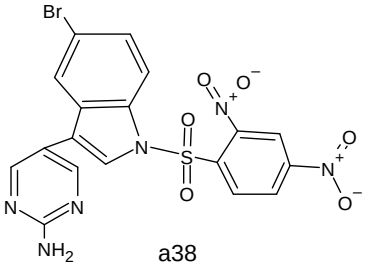

a34


a35


a36

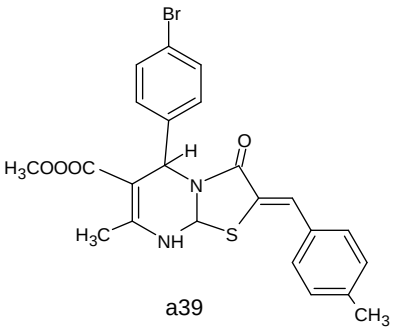
`A series of *N*-aryl and heteroaryl sulfonamide derivatives of meridianins were prepared by Yadav et al. and screened for its antimalarial activity against D6 and W2 strains of *Plasmodium falciparum*. Especially, compounds, **a37** and **a38** displayed promising antiplasmodial activity and comparable to the standard drugs[LXIII].

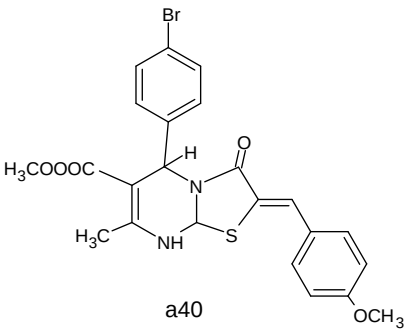

a37

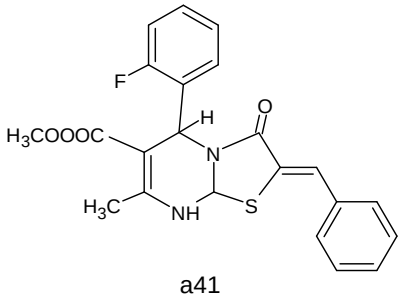

a38

Anti-inflammatory activity

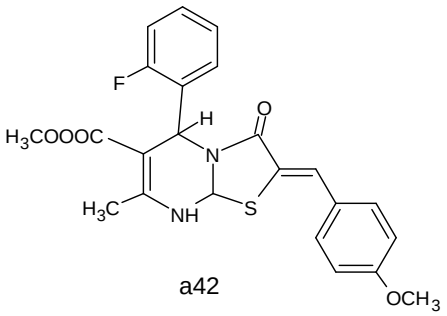
Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutics, primarily for the treatment of pain, rheumatic arthritis and various types of inflammatory conditions. However, their use is mainly restricted by their well known and serious adverse gastrointestinal side effects such as gastroduodenal erosions, ulcerations and nephrotoxicity[LXIV].Tozkoparan et al. synthesized a new class of 2-benzylidene- 7-methyl-3-oxo-5-(substituted phenyl)-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylic acid methyl esters and evaluated its anti-inflammatory activity by carrageenan induced edema test using indomethacin as reference drug. Test results revealed that compounds, **a39, a40, a41** and **a42** exerted moderate anti-inflammatory activity at the 100 mg/kg dose level compared with indomethacin[LXV].


a39


a40

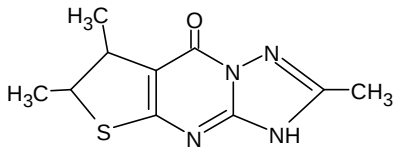


a41

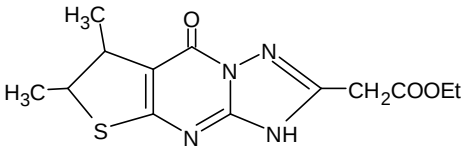


a42

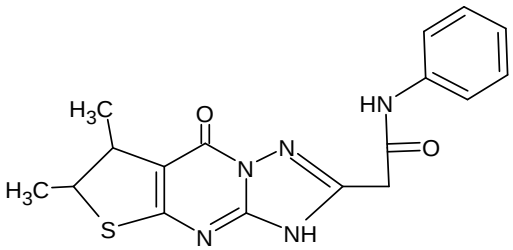
The thienotriazolo pyrimidine derivatives, **a41, a42** and **a43** were proved to display distinctive anti-inflammatory activity at the acute and sub acute models as well as good analgesic profile with a delayed onset of action[LXVI]



a41

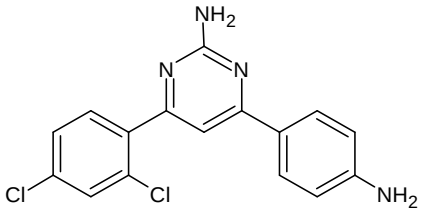


a42

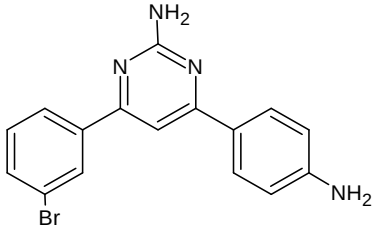


a43

Yejella and Atla, synthesized a new series of 2,4,6-trisubstituted pyrimidines and screened its in vivo anti-inflammatory activity by carrageenan induced rat paw edema model. Compounds, **a44**: 2-amino-4-(4-aminophenyl)-6-(2,4-dichlorophenyl)pyrimidine and **a45**:Compound EC50 (μM) 2-amino-4-(4-aminophenyl)-6-(3-bromophenyl)pyrimidine were found to be the most potent anti-inflammatory agents compared with ibuprofe[LXVI].

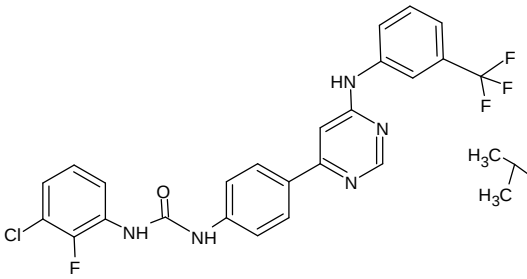


a44

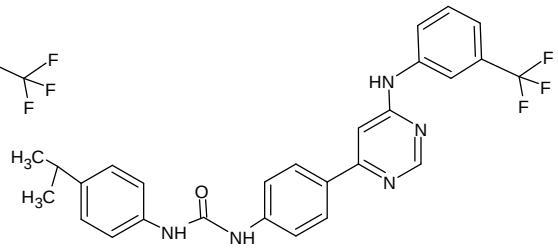


a45

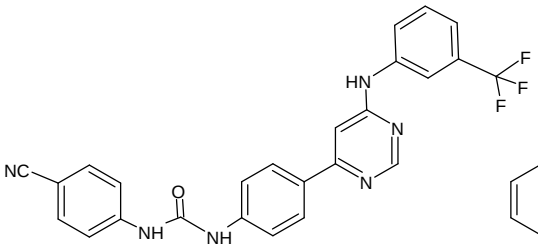
Keche et al. developed a new series of novel 4-(3-(trifluoromethyl) phenylamino-6-(4-(3-arylureiodo/arylthioureido/ arylsulfonamido)-pyrimidine derivatives by the sequential Suzuki cross coupling and screened for their anti-inflammatory activity. Among all the synthesized derivatives, compounds, **a46, a47, a48, a49, a50** and **a51** were found to have moderate to potent anti-inflammatory activity and compared to dexamethasone used as reference drug [LXVII].



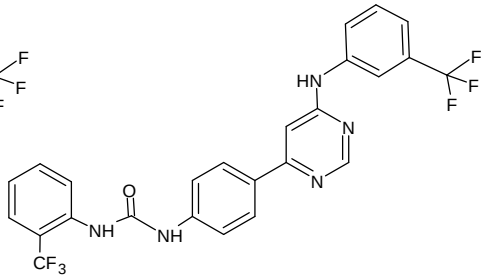
a46



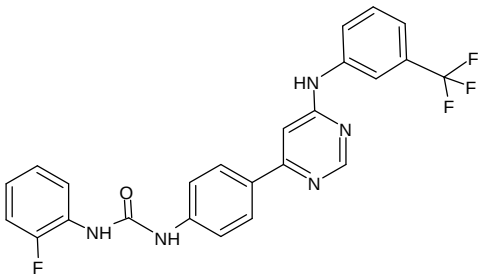
a47



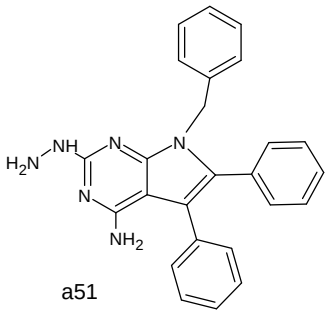
a48



a49



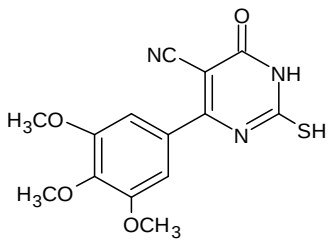
a50



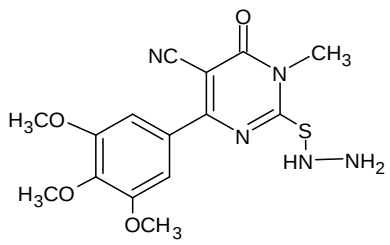
a51

Antioxidant activity

Oxidative stress seems to play a significant role in various human diseases, including cancers. Antioxidant compounds are the agents that neutralize free radicals, which scavenge reactive oxygen species, may have potent value in preventing the onset and propagation of oxidative diseases such as neurovascular, cardiovascular diseases. Pyrimidine and its derivatives have recently attracted the attention of medicinal chemists in exploring their potential as antioxidant agents Bhalgat et al. developed a new class of novel pyrimidines and its triazole fused derivatives and investigated its in vitro antioxidant by various methods as scavenging of hydrogen peroxide, scavenging of nitric oxide radical and lipid per oxidation inhibitory activity. Compounds, **a52** showed good antioxidant activity as compared to standard by scavenging of nitric oxide radical and hydrogen peroxide, while **a53** showed most potent antioxidant activity by scavenging of nitric oxide[LXIX].

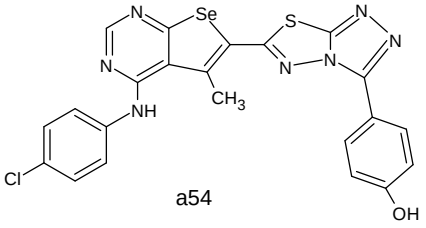


a52

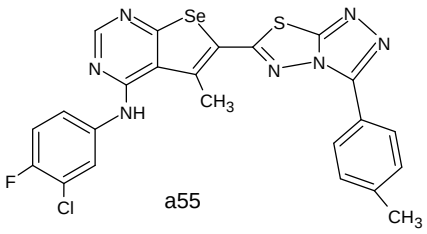


a53

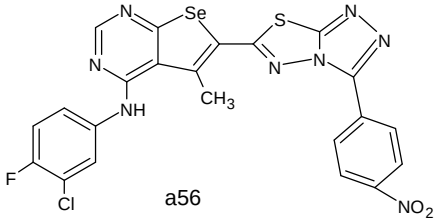
Kotaiah et al. synthesized new molecules of novel 1,2,4- triazolo[3,4-*b*][1,3,4]thiadiazol-6-yl)selenopheno[2,3-*d*] pyrimidines with substituted anilines and benzoic acid. The antioxidant activity of the synthesized compounds was evaluated by DPPH, NO and H_2O_2 radical scavenging methods. In this series, compounds, **a54, a55** and **a56** showed promising antioxidant activity compared to standard drug[LXX]



a54

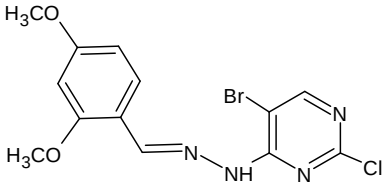


a55

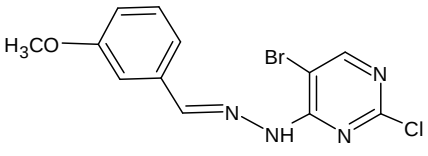


a56

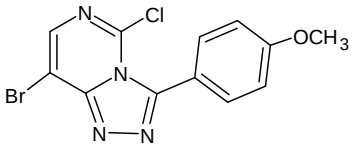
Mohana et al. reported a new series of pyrimidine derivatives and evaluated its antioxidant activity by DPPH method. The structures of all the new compounds are established on the basis of FT-IR, 1H-NMR and Mass spectral data. All the compounds showed DPPH radical scavenging activity, whereas, compounds, **a57, a58** and **a59** exhibited best radical scavengers due to presence of electron donating methoxy group at different position (*ortho*, *meta* and *para*)[LXXI].



a57

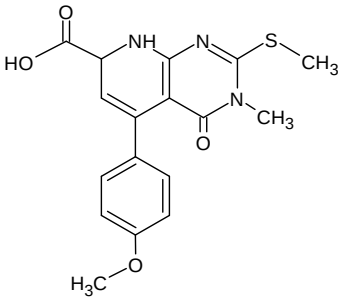


a58

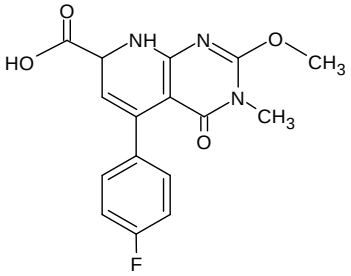


a59

Quiroga et al. developed a new library of 5-aryl-4-oxo- 3,4,5,8-tetrahydropyrido[2,3-*d*] pyrimidine-7-carboxylic acids and carried out their antioxidant activity by DPPH (1,1-diphenyl-2-picryl-hydrazyl) radical scavenging assay. Compounds **a60** and **a61** showed antioxidant properties and compared to standard drugs[LXXII].



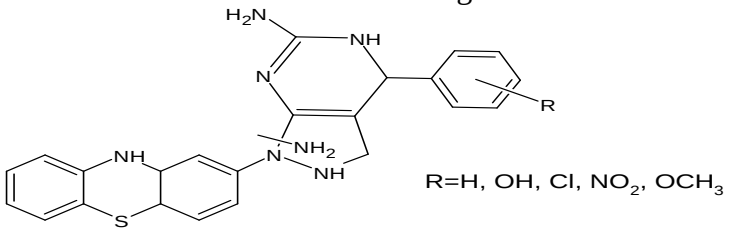
a60



a61

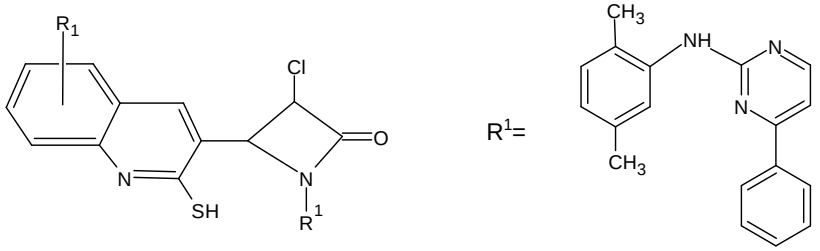
Antitubercular activity

Siddiqui et al.[LXXIII] had synthesized a series of novel dihydropyrazolo [3,4- d] pyrimidine derivatives (**a62**) bearing a phenothiazine nucleus were synthesized in excellent yields via a modified biginelli multicomponent reaction. New synthesized compounds were screened for antitubercular activity. The new compounds were characterized by infrared (IR), ^{1}H nuclear magnetic resonance (NMR), 13C NMR, mass spectra, and elemental analysis followed by antimycobacterial screening. Compound 4-(4-chlorophenyl)-3 methyl-1-(10 H Phenothiazin-2-yl) -4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6 amine showed most pronounced activity against Mycobacterium tuberculosis with minimum inhibitory concentration of 0.02 lg/mL, and compare with first line anti-tubercular drug isoniazid.



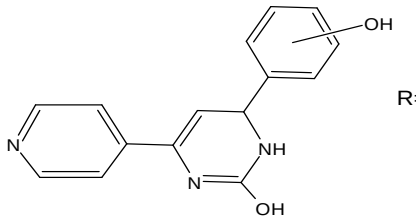
a62

Chandrashekaraiah et al[LXXIV] reported a series of 1-(3-(4-(pyridin-3-yl) pyrimidin-2-ylamino)-4-methylphenyl)-3-chloro-4-(2-mercaptoquinolin-3-yl) azetidin-2-one (**a63**) have been synthesized. The newly synthesized analogs were examined in-vitro for antituberculosis activity against M. tuberculosis. The class of newly synthesized analogs displayed the highest inhibition at a constant concentration level (6.25 μg/mL) against M. tuberculosis H37Rv.



a63

Kachroo et al[LXXV] has reported synthesis of chalcones by the reaction of 4-acetylpyridine with various aromatic and heteroaromatic aldehydes and further, chalcones derivatives were cyclized to pyrimidine analogs using thiourea, urea, and guanidine hydrochloride. The newly synthesized compounds (**a64**) have been characterized by ultraviolet, IR, ^{1} HNMR, ^{13}CNMR, mass spectra. It was found that 2 amino pyrimidine analog bearing 4-fluoro substitution on phenyl ring has exhibited excellent antitubercular activity.

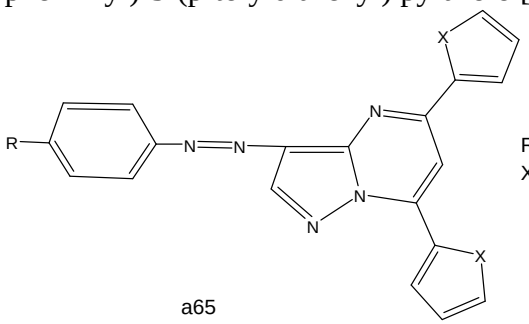


R= Cl, CH_3, OCH_3, F

a64

Antifungal activity

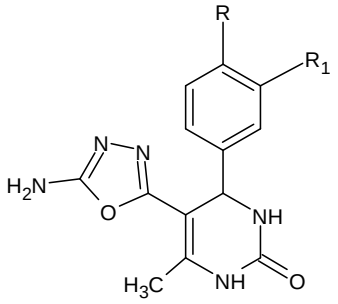
Ishak *et al*.[lXXVI] carried out the synthesis of pyrazolo-[1, 5-a] pyrimidine and pyrimidine derivatives and screened them for antifungal activities. New series of pyrazolo-[1, 5-a] pyrimidines (**a65**) were also screened for their antifungal activity against (*Candida albicans* [RCMB0005003], *Aspergillus fumigates* [RCMB002006], *Geotrichum candidum* [052008], *Syncephlastrum racemosum* [005004]). The compound 5,7-di(furan 2-yl)-3-(p-tolydiazenyl)pyrazolo[1,5-a]pyrimidin-2-amine showed better antimicrobial activity than 5-(furan-2-yl)-7-(thiophen-2-yl)-3-(p-tolyldiazenyl) pyrazolo [1,5-a] pyrimidin-2-amine.



R=H, Cl, OCH_3, CH_3
X=S, O

a65

Andrews and Mansur[LXXVII] had synthesized a series of pyrimidine bearing 1, 3, 4-oxadiazole derivatives and screened them for antifungal activity. All the structures of the newly synthesized compounds (**a66**) have been supported by IR, 1H-NMR, 13C-NMR, GC-MS, and CHN analysis. Newly synthesized pyrimidine derivatives were screened for their antifungal activity *in-vitro* against the species of *C. albicans*, *Penicillium* sps., *and A. niger*, using agar well disk diffusion method and using amphotericin-B as the standard drug.



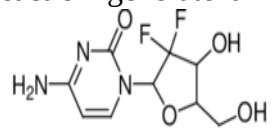
R= H, Cl, OH, $N(CH_3)_2$
R_1= HNO_2

a66

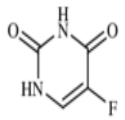
Marketed drugs containing pyrimidine derivatives

Conclusions

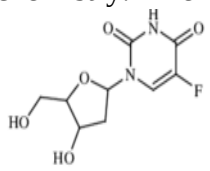
In conclusion, numerous methods for the synthesis of pyrimidine and also their diverse reaction generate an enormous scope in the field of medicinal chemistry. The utility of



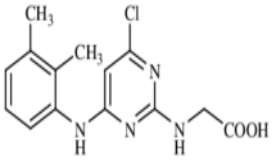
Gemcitabine
(Anti cancer)



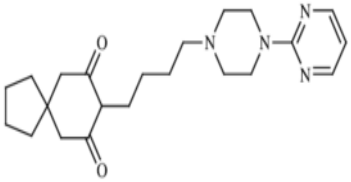
5-Fluorouracil
(Anti cancer)



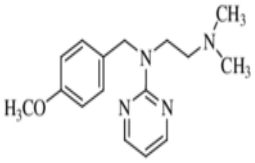
Floxuridine
(Anti cancer)



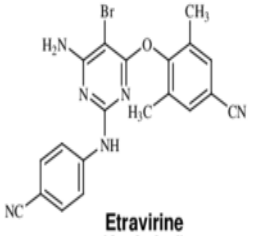
Aronixil
(Anti-hyperlipidemic)



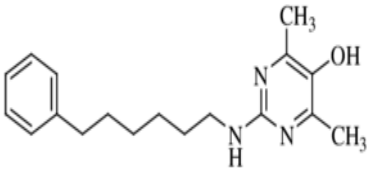
Buspirone
(Anti psycotic)



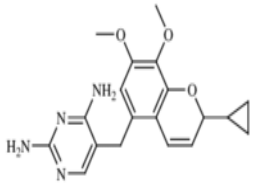
Thonzylamine
(Anti histaminic)



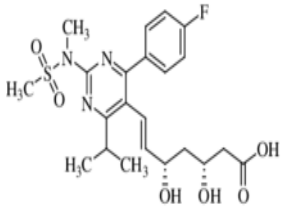
Etravirine
(Anti viral)



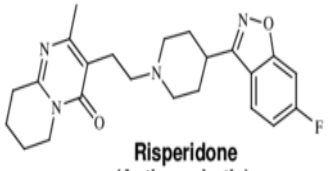
Enazadrem
(Anti psoriatic)



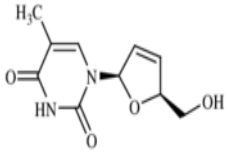
Iclaprim
(Antibiotic)



Rosuvastatin
(Anti lipidemic)



Risperidone
(Anti psychotic)



Stavudine
(Anti HIV)

pyrimidines as synthon for various biologically active compounds has given impetus to these studies. Their modes of synthesis and biological potentials i.e. antimicrobial, anticancer, anti-inflammatory, antioxidant, antituberculosis, antifungal and antimalarial of pyrimidine derivatives are summarized. Pyrimidine is the important heterocyclic compound as they are being an essential constituent of cells and large number of marketed drugs. The biological activities of the pyrimidine derivatives indicated the maneuverability and versatility, which offer the medicinal chemist a continued interest in the pyrimidine skeleton in medicinal field.

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