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Current status and future scenario of pyrimidine derivatives having antimicrobial potential

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ABSTRACT

Day by day there has been incerasing consumption of various antibiotics for the treatment of microbial infections which leads to emergence of multi-drug resistant microbial pathogens. Therefore, there is an urgent demand for research and synthesis of novel of antimicrobial agents having different mode of action which should be effective against various types of bacteria and fungi to solve the problem of microbial resistance. Pyrimidine derivatives are known to have broad spectrum of pharmacological activities, especially potent antimicrobial activities. This review article is an attempt to provide valuable information on antibacterial and antifungal potential of pyrimidine derivatives which may help to medicinal chemists in the development of new class of antimicrobial agents for effective treatment of microbial diseases.

Keywords: pyrimidine, antibacterial, antifungal activity.

INTODUCTION

It has been observed that spite of mounting problems of resistance to antimicrobial agents [1], the number of innovative antibiotics being brought to the pharmaceutical market have been reduced drastically in recent times for example only five new antibacterial agents are accepted for scientific purpose in the USA [2]. Further, there is shortage of novel antibiotics and appearance of multi-drug-conflicting microbes being some of the major challenges for drug proposal and expansion of narrative antimicrobial agents. Gram-negative bacteria are particularly intricate to eradicate as they have an extra outer film permeability obstruction that antimicrobial compounds require to overcome to be successful, in addition to recurrently possessing numerous efflux pumps and intention-modifying enzymes [3]. Various types of microbes like bacteria, fungi and virus are responsible for lethal microbial infections for example tuberculosis, anthrax, typhoid, cholera, diphtheria, bacterial meningitis, syphilis, whooping cough pneumonia, bubonic plague, toxoplasmosis and candidiasis or histoplasmosis [4].

Pyrimidine is a heterocyclic ring system having two nitrogen atoms at positions 1 and 3 in the ring **(Fig.1)** [5]. Amongst a wide variety of heterocycles that have been explored for developing medicinally important molecules, pyrimidine derivatives occupy an important place in the present day therapeutics. They are reported to possess a broad spectrum of pharmacological activities such as antimicrobial, antitubercular, anti-inflammatory, anticancer, antiviral and antimalarial properties which describes the significance of this heterocyclic nucleus in current medicinal chemistry [6].

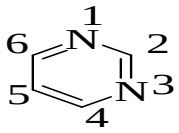
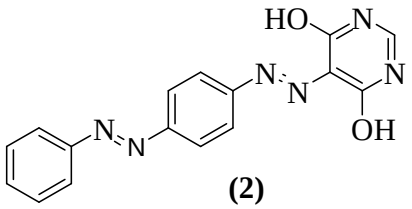


Fig: (1)

Antimicrobial Activities

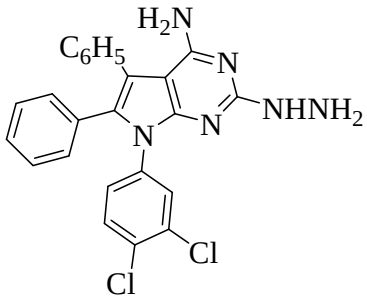
According to the recent literature survey, it may be observed that novel pyrimidine derivatives are found to have potent antimicrobial activities and this information has been summarized in this section as given below:

Yazdanbakhsh *et al* reported the synthesis of 4, 6-dihydroxypyrimidines **(2)** and evaluated for their antibacterial activity against *Salmonella typhimurium, Micrococcus luteus, Bacillus subtilis* and *Pseudomonas aeruginosa* at concentration of 125µg/ml by using Tetracycline and Erythromycin as standard drugs. One compound showed good antibacterial activity against *B. subtilis* and *P. aeruginosa* when compared with standard drugs [7].



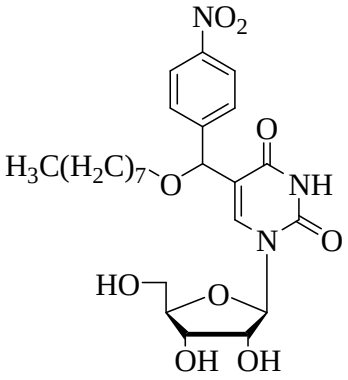
(2)

A series of 8-Aryl-pyrrolo, thiazolo pyrimidine derivatives **(3)** prepared by Mohameda *et al*. All newly synthesized compounds were examined for their antibacterial activity against *Staphylococcus pyrogens* and antifungal activity against *Candida albicans* and *Aspergillus flavus* according to cup plate method at a concentration of 0.035mg/ml by using Chloramphenicol and Flucanazole as standards for antibacterial and antifungal activities respectively. Some compounds showed promising antimicrobial activities when compared with their respective standard drugs [8].



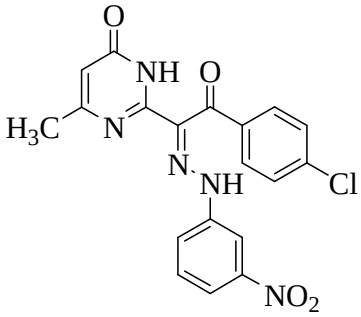
(3)

A series of uridine analogues **(4)** was synthesized by Brulikova *et al* and tested for their antibacterial activity against *Pseudomonas aerugenosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Candida albicans.* Chloramphenicol and Flucanazole were used as standards for comparison of antibacterial and antifungal activities respectively. Some compounds demonstrated significant antibacterial activity against *P. aerugenosa* and *S. aureus* whereas other compounds exhibited appreciable antifungal activity against *A. niger* and C. *albicans* when compared with their respective standard drugs [9].



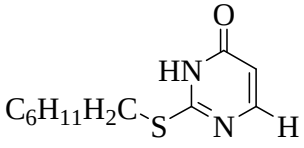
(4)

Edrees *et al* prepared a series of 2-[N-aryl-2-oxo-2-(4-chlorophenyl) ethanehydrazonoyl]-6-methyl-4(3*H*) pyrimidinones derivatives **(5)**. All newly synthesized compounds were screened for their potent antibacterial activity against *Pseudomonas aerugenosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Candida albicans*. Chloramphenicol and Flucanazole were used as standards. Some compounds showed promising antibacterial activity against *P. aerugenosa* and *S. aureus* whereas other compounds exhibited significant antifungal activity against *A. niger* and C. *albicans*. One compound showed good antimicrobial activity at minimum inhibitory concentration of 15.10µg/mL against the bacterial stains [10].



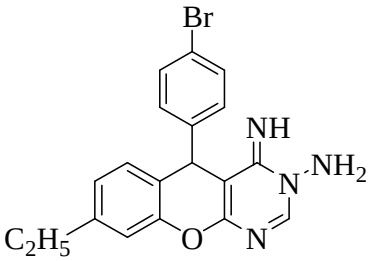
(5)

Prachayasittikul *et al* reported thiopyrimidines derivatives **(6)** as potential therapeutics achieved novel analogs of bioactive thiopyrimidines-4-(3*H*)-ones and investigated their antibacterial activity against *Pseudomonas aerugenosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Candida albicans*. Chloramphenicol and Flucanazole were used as standards for comparison of antibacterial and antifungal activities respectively. Some compounds showed promising antibacterial activity against *P. aerugenosa* and *S. aureus* and antifungal activity against *A. niger* and C. *albicans* and exhibited potent antimicrobial activity. One compound showed complete inhibition against *Streptococcus pyogenes* and *Branhamella catarrhalis* as well as antifungal action against *Candida albicans* and it was found to be the most potent antimicrobial compound when compared with standard drugs [11].



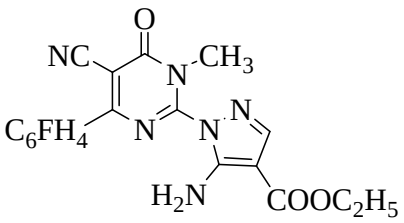
(6)

Sabry *et al* provided a series of compounds as 12*H*-Chromeno pyrimidine derivatives **(7)** and their *in-vitro* evaluation for antibacterial activity against gram positive bacteria (*Enterococcus fecalis ATCC-29212, Bacillus subtilis)* and gram negative bacteria (*Escherichia coli ATCC-25923, Pseudomonas aeruginosa ATCC-27853*) and antifungal activity against (*Candida albicans NLTM-3431, Aspergillus Niger)* were compared with their respective standard drugs Amoxycillin and Griseofulvin. Some compounds showed significant antimicrobial activity when compared with standard drugs. A new compound was found having potent antimicrobial activities against *Salmonella typhimurium, Micrococcus luteus, Bacillus subtilis* and *Pseudomonas aeruginosa* when compared with standard drug [12].



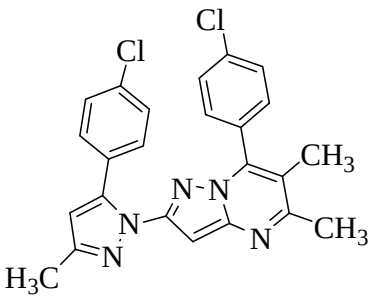
(7)

Ramesh *et al* synthesized novel dihydropyrimidines derivatives **(8)** and their *in-vitro* evaluation for antibacterial activity against gram positive bacteria (*Enterococcus fecalis ATCC-29212, Bacillus subtilis)* and gram negative bacteria (*Escherichia coli ATCC-25923, Pseudomonas aeruginosa ATCC-27853*) and antifungal activity against (*Candida albicans NLTM-3431, Aspergillus niger)* were compared with their respective standard drugs Amoxycillin and Griseofulvin. Some compounds showed significant antimicrobial activity when compared with standard drug. One of these novel derivative showed potent *in vitro* antimicrobial activity at concentration of 15.10µg/mL as compared to the standard drug streptomycin and also reported antibacterial activity [13].



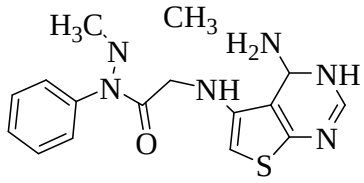
(8)

An efficient and environmental benign regioselective new pyrazol-10-ylpyrazolo pyrimidines derivatives **(9)** were synthesized by Aggarwal *et al*. All compounds were screened for their antibacterial activity against gram-positive and gram-negative bacteria and antifungal activity against four phytopathogenic fungi. Two compounds manifested rather broad antibacterial activity than standard antibiotics. One lead compound at concentration of 10 mg/ml and 200 mg/ml exhibited equipotent or more potent antimicrobial and antifungal activities against all tested microorganisms when compared with standard drugs Ciprofloxacin and Fluconazole [14].



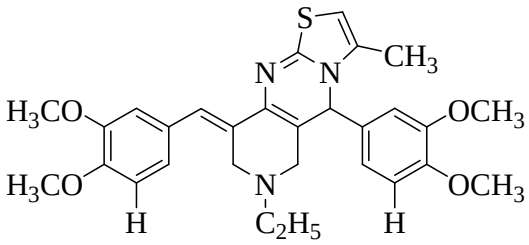
(9)

A novel series of thienopyrimidine derivatives **(10)** were synthesized by Aly *et al* and investigated their antibacterial activity against *Pseudomonas aerugenosa* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Candida albicans.* Chloramphenicol and Flucanazole were used as standards for comparison of antibacterial and antifungal activities. Some compounds showed promising antibacterial activity against *P. aerugenosa* and *S. aureus* whereas other compounds exhibited significant antifungal activity against *A. niger* and C. *albicans.* One compound was tested against antimicrobial activities which exhibited higher and promising biological activities when compared with respective standard drugs [15].



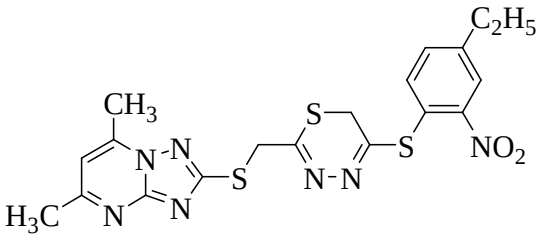
(10)

A novel series of thiazolo quinazoline and pyrido thiazolo pyrimidine analogues **(11)** were designed and synthesized by Al-Omary *et al.* Newly synthesized compounds were screened *in-vitro* for their antimicrobial activity against varieties of bacterial strains such *Staphylococcus epidermidis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa* and fungal stain *Aspergillus niger* by using as Ampicillin and Gentamycin as standard drugs for antibacterial and antifungal activities respectively. One compound showed appreciable antimicrobial activity when compared with standard drugs. Some compounds were evaluated for their *in-vitro* antimicrobial activity against all types of bacterias and compared with standard drugs Ampicillin and Gentamycin [16].



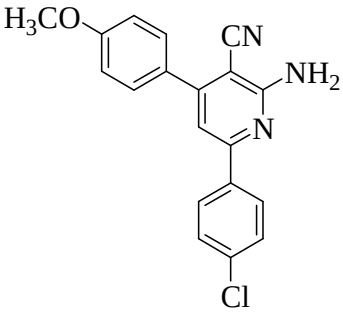
(11)

A series of novel 1,3,4-thiadiazole derivatives **(12)** bearing 1,2,4-triazolo pyrimidine moiety were synthesized by Zhang *et al*. All compounds were assayed for their antimicrobial activities against five fungi stains and four bacteria stains. The preliminary results indicated that some compounds showed good antifungal activities against *Physaclospora piricola, Rhizoctonia solani* and *Cercospora beticola*. One compound showed better antibacterial activity against Gram-negative bacterial stains and Gram-positive bacterial stains *Pseudomonas fluorescence and Escherichia coli* as in comparison of standard drugs Ciprofloxacin and Griseofulvin [17].



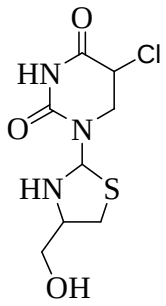
(12)

Kumar *et al* synthesized new series of substituted 4, 6-substituted diphenylpyrimidin-2-amine derivatives **(13)** and were investigated for their antibacterial activity against *Bacillilus subtilis, Escherichia coli, Pseudomonas* species and *Staphylococcus aureus* by using standard drug Ofloxacin. One compound displayed potent antimicrobial activity against gram negative bacteria *(E. coli)* and gram positive bacteria *(S. aureus)* on comparison with the standard drug [18].



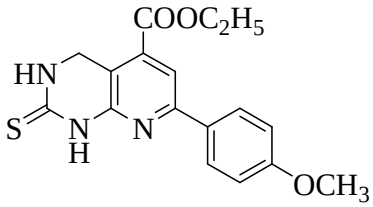
(13)

Sriharsha *et al* synthesised a new class of 1,3-thiazolidine nucleoside analogues coupled with the pyrimidine bases **(14)** like uracil and thymine etc. The antibacterial activity of the novel 1,3-thiazolidine pyrimidine nucleoside analogues were highlighted and screened for their antibacterial activity *in-vitro* against *Pseudomonas aeruginosa, Escherichia coli* as Gram-negative bacteria and *Staphylococcus aureus, Serratia, Enterobacter, Acetobacter* as Gram positive bacteria. Few compounds showed remarkable activity towards the gram positive bacteria *Staphylococcus, Enterobacter* and Gram negative bacteria *Pseudomonas aeruginosa, Escherichia*. One compound with free NH group in the pyrimidine moiety showed significant biological activity against the bacterial stains *Streptococcus pyogenes* and *Branhamella catarrhalis* as compared with standard drug Ampicillin [19].



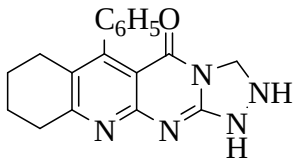
(14)

Mohamed *et al* synthesized pyrido pyrimidines derivatives **(15)**. The *in vitro* antimicrobial activity of some of the newly synthesized compounds was examined. All the tested compounds proved to be active as antibacterial and antifungal agents. One compound showed potent activity against various bacteria tested in comparison of standard drugs Chloremphenicol and Nystatin [20].



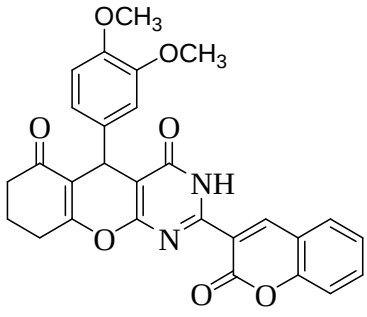
(15)

El-Gazza *et al* reported a novel series of pyrimido quinolines, triazolo pyrimido quinolines, pyrazol pyrimido quinolines and 2-pyrazolylpyrimido quinolines derivatives **(16).** Synthesized compounds were tested for antibacterial activity against various bacteria and fungi species at concentration of 20µg/mL. One Compound was found with high antifungal activity toward the fungal stains as compared with the reference drugs Nystatin and Nalidixic acid [21].



(16)

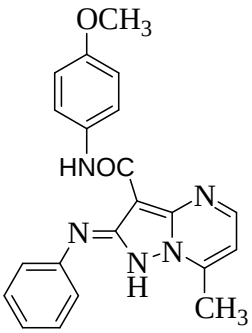
Banothu *et al* reported a series of 8,9-dihydro-2-(2-oxo-2*H*-chromen-3-yl)-5-aryl-3*H*-chromeno pyrimidine-4,6-diones derivatives **(17)**. All the synthesized compounds were evaluated for their *in vitro* antimicrobial activity against different bacterial and fungal stains. One compound showed potent antimicrobial activity as it displayed MIC value of 12.5 mg/mL and showed excellent antibacterial activity against *B. subtilis* and *E. coli* on par with standard drug Ciprofloxacin whereas other compound showed MIC value of 25 mg/mL and it showed good antifungal activity against *C. albicans* as compared with standard drug Amphotericin-B [22].



(17)

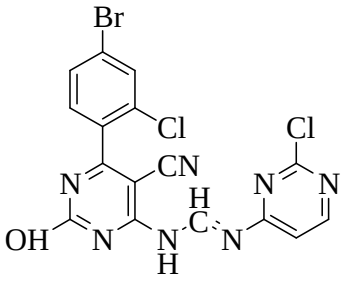
Hussein *et al* achieved an easy and efficient route for the synthesis of pyrimido pyrimidine derivatives **(18)** and evaluated *in vitro* antibacterial activity against *Escherichia coli*, *Micrococus luteus* and *Staphylococcus aureus* and antifungal activity against *Aspergellius flavus*, *Aspergillus niger* and *Curvularia lunata* by using standard drugs for antibacterial and antifungal activities. Some compounds showed promising antimicrobial activities as compared with their respective standard drugs. The potent antimicrobial screening of one derivative was noted against the tested

microorganisms *C. albicans*, *B. subtilis* and *E. coli* and found on par with standard drugs Chloramphenicol and Fluconazole [23].



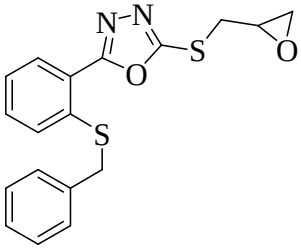
(18)

A series of novel (E)-N-(2-chloropyrimidin-4-yl)-N-(5-cyano-2-hydroxy-6-phenylpyrimidin-4-yl) formamidine derivatives **(19)** was synthesized by Mallikarjunaswamy *et al* and *in vitro* antimicrobial activity was evaluated. Antimicrobial data revealed that among all the compounds screened against bacteria like *Bacillus subtilis*, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* and fungal stains like *Alternaria solani* and *Fusarium oseysporum*, one compound was found to have promising antimicrobial activity against all the selected pathogenic bacteria and fungi when compared with standard drug Amoxicillin [24].



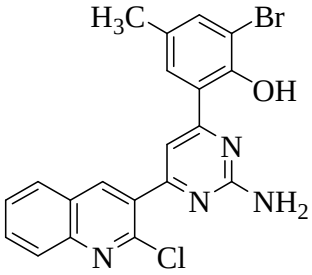
(19)

A novel series of 5-(2-benzylsulfanyl-pyridin-3-yl)-2-(substituted)-sulfanyl-1,3,4-oxadiazoles derivatives **(20)** were synthesized by Patel *et al.* All compounds were evaluated for their antimicrobial activities. The compound with benzothiazole moiety showed promising activity against *Escherichia coli* compared to Ampicillin as standard drug. The antibacterial screening results reveal that most of the final compounds showed good bacterial inhibition against *S. aureus*. One compound was bearing epichlorohydrin exhibited highest activity against *S. aureus and S. pyogenes* [25].



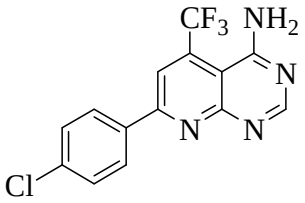
(20)

A series of novel 2-(5-bromo-2-chloro-pyrimidin-4-ylsulfanyl)-4-methoxy-phenylamine derivatives **(21)** were synthesized by Mallikarjunaswamy *et al*. and observed an elevated antibacterial activity against Gram positive (zone of inhibition 29–33 mm) and Gram negative (zone of inhibition 32–33 mm) bacteria. Some compounds showed good antibacterial activity against all the tested organisms. One compound showed most potent *in-vitro* antimicrobial activity as compared to standard drugs Gentamicin, Bacteriomycin and Nystatin [26].



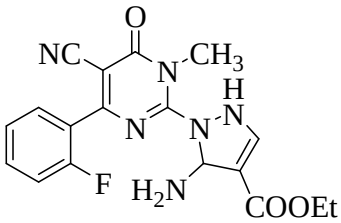
(21)

Kanth *et al* synthesized novel pyrido pyrimidines derivatives **(22)** and evaluated *in-vitro* antibacterial activity against *Escherichia coli, Micrococus luteus* and *Staphylococcus aureus* and antifungal activity against *Aspergellius flavus, Aspergillus niger* and *Curvularia lunata* by using Chloramphenicol and Fluconazole as standard drugs for antibacterial and antifungal activities respectively. Some compounds showed promising antimicrobial activities as compared with their respective standard drugs. All compounds were screened against Gram positive and negative bacteria *in vitro*. Compounds showed potent activity against all species of Gram positive bacteria and Gram negative bacteria. Both compounds were also active against *Pseudomonas aeruginosa* at the maximum concentration of 200 µg/ ml as compared to standard drugs [27].



(22)

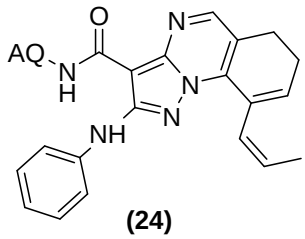
Narayana *et al* synthesized novel dihydropyrimidines derivatives **(23)** and screened them for their antimicrobial activities. One of novel compounds showed potent *in vitro* antibacterial and antifungal activity having MIC value of 14.72 µg/ml against all species of Gram positive bacteria and Gram negative bacteria like *Bacillus subtilis, Escherichia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa* and fungal stains like *Alternaria solani* and *Fusarium oseysporum* and compared with standard drugs Ciprofloxacin and Fluconazole [28].



(23)

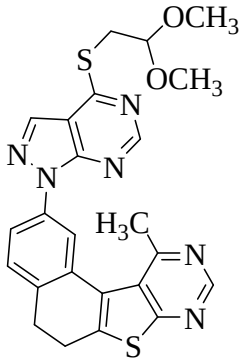
Gouda *et al* reported that 3-aminopyrazole utilized as key intermediate for the synthesis of pyrazolo pyrimidine derivatives **(24)** and evaluated them against *Pseudomonas aeroginosa, Escherichia coli* as Gram negative bacteria and *Staphylococcus aureus, Treptococcus pneumonia* and *Klebsila pneumonia* as Gram-positive bacteria. One

compound was evaluated as potent antimicrobial agent as compared to standard drugs Ampicillin, Chloremphenicol and Cloxacillin. One compound also exhibited promising activity with maximum zone of inhibition value of 25mm against various bacterial stains [29].



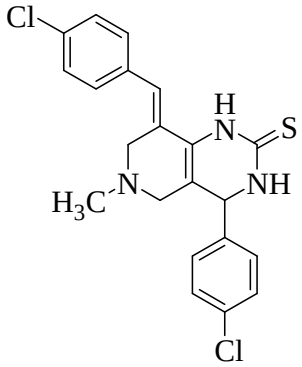
(24)

Rashad *et al* substituted some acyclic S-nucleosides of pyrazolo pyrimidine derivatives **(25)** and tested for their antimicrobial activity against bacteria *Xanthomonas*, *Erwinia amylovora*, and filamentous fungi *Pyrenophora avenae***,** *Fusarium graminearum.* One compound showed promising antimicrobial activity as compared to standard drug [30].



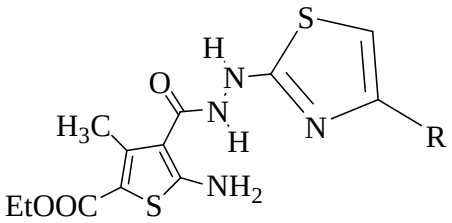
(25)

Mohamed *et al* synthesized a series of pyrazolopyridine and pyridopyrimidine derivatives **(26)**. Some of the tested compounds, especially with a fluorine substituent at the para-position in the phenyl ring and those with a pyridopyrimidine-2-thione with a free –NH or –SH, exhibited greater *in vitro* antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans*. Some of the test compounds were found to have excellent to moderate antimicrobial activities when compared with standard drug Nystatin [31].



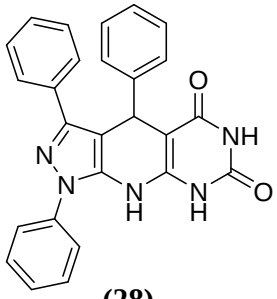
(26)

Two series of 5-ethyl-2-amino-3-pyrazolyl-4-methylthiophenecarboxylate and 2-thioxo-N3-aminothieno pyrimidines derivatives **(27)** were prepared by Hafez *et al* and evaluated as antimicrobial agent. All compounds were screened for antimicrobial activity, one compound showed the highest activity against all bacteria. Two compounds exhibited stronger activity than Ampicillin against *B. cereus* and *S. typhi* [32].



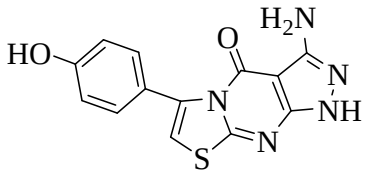
(27)

Bazgira *et al* synthesized pyrazolo pyrido pyrimidine-dione derivatives **(28)** and evaluated their antibacterial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans*. Some of the test compounds were found to have excellent to moderate antimicrobial activities when compared with their respective standard drugs. One compound was found to have potent antibacterial activity as compared with standard drug Ciprofloxacin [33].



(28)

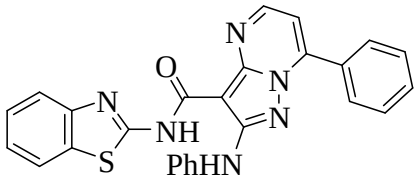
Some novel pyrazolo thiazolo pyrimidin-4-one derivatives **(29)** were prepared by Khobragade *et al*. All the compounds of the series were screened for their antibacterial and antifungal activities against bacterias viz. *Bacillus megaterium* (MTCC 1684), *Bacillus subtilis* (MTCC 1789), *Klebsiella pneumoniae* (NCIM 2957), *Staphylococcus aureus* (MTCC 96), *Pseudomonas aeruginosa* (MTCC 2488), *Proteus vulgaris* (MTCC 1771), *Escherichia coli* (MTCC 1650) and *Serratia marcescens* (MTCC 86) and fungi viz. *Trichoderma viridae* (MTCC167), *Penicillium chrysogenum* (MTCC1996), *Aspergillus flavus* (MTCC 2501), *Aspergillus niger* (MTCC 1781) and *Candida albicans*. The result revealed that one compound showed significant antimicrobial activities as compared to respective standard drugs Tetracycline and Nystatin [34].



(29)

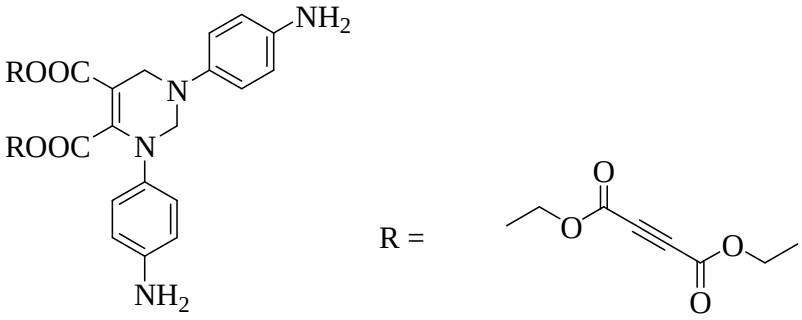
Bondock *et al* found a new class of antimicrobial agents containing pyrazolo pyrimidine derivatives **(30)**. All compounds were screened for their antibacterial activity against Gram-positive bacteria *(Staphylococcus aureus and Streptococcus pyogenes)*, Gram-negative bacteria *(Pseudomonas phaseolicola and Pseudomonas fluorescens)* and antifungal activity against *Fusarium oxysporum* and *Aspergillus fumigatus*. One compound showed potent activity when compared with Chloroamphenicol as a standard drug against *S. aureus* (MIC = 3.125 mg/mL), *S. pyogenes*.

Pyrazolo pyrimidine derivative was found to exhibit the most potent *in vitro* antifungal activity with MIC at 6.25 mg/mL against *A. fumigates* [35].



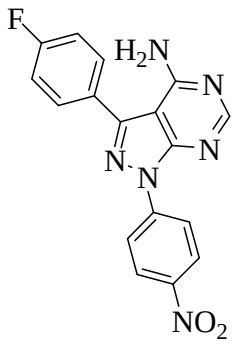
(30)

Darandale *et al* reported 1,3,4,5-tetrasubstituted 1,2,3,6-tetrahydropyrimidines derivatives **(31)** having promising antibacterial and antifungal activities and screened for their antibacterial activity against *Staphylococcus pyrogens* and antifungal activity against *Candida albicans* and *Aspergillus flavus* according to cup plate method at different concentrations by using Chloramphenicol and Flucanazole as standards for antibacterial and antifungal activities. The antimicrobial activity data revealed that one compound was most potent as compared to standard drugs. These compounds were found to be most active against the tested fungal and bacterial stains, having MIC values (15–60 µg/mL for bacteria and 12.5–50 µg/mL for fungus) compatible with standard drugs [36].



(31) Diethylbut-2-ynedioate

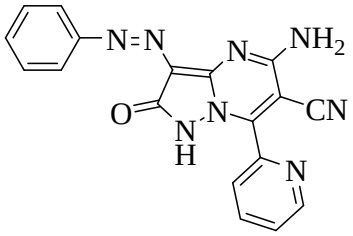
Abunada *et al* obtained pyrazolo pyrimidin-4(3*H*)one derivatives **(32)** against a selection of Gram-positive cocci, Gram-negative rods and yeasts. Some compounds showed antibacterial activity against Gram-positive bacteria having MIC values in range of 50 to 200 µg/mL. One of these compounds also exhibited potent antifungal activity against the *Candida* stains like *C. albicans* and *C. parapsilosis* as compared with standard drug [37].



(32)

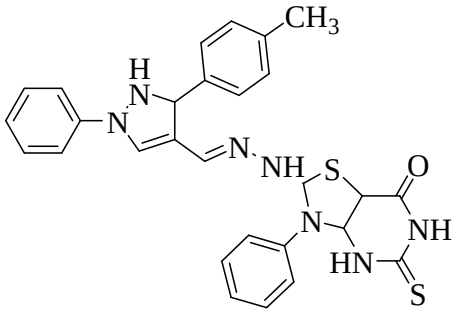
El-Gaby *et al* prepared some novel substituted pyrazol pyrimidines derivatives **(33)**. Most of these compounds were also tested *in vitro* for their antibacterial activity against Gram positive and Gram negative bacteria. Most of the

synthesized compounds were found to possess high antibacterial activity towards *S. marcescens* (IMRU-70), *S. aureus* (NCTC 7447) as compared to the Streptomycin as a reference drug [38].



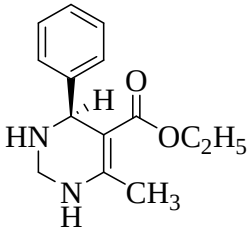
(33)

Bekhit *et al* synthesized a novel series of structurally related 1*H*-pyrazolyl of thiazolo pyrimidines derivatives **(34)**. Newly synthesized compounds were evaluated for their *in vitro* antimicrobial activity against *Escherichia coli*, a Gram negative bacteria, *Staphylococcus aureus* as Gram positive bacteria, and *Candida albicans* as a representative of fungi. The results revealed that most of them displayed appreciable antibacterial activities when compared with Ampicillin, especially against *S. aureus*. One compound was the most potent derivative having pronounced antibacterial activity comparable to Ampicillin [39].



(34)

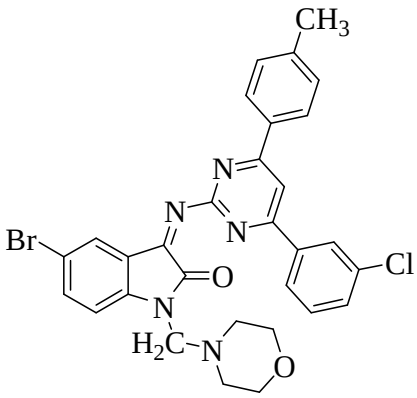
Gaikwada *et al* described the synthesis of dihydropyrimidones derivatives **(35)** and screened for their antibacterial activity against *Staphylococcus pyrogens* and antifungal activity against *Candida albicans* and *Aspergillus flavus* according to cup plate method at a concentration of 0.005mol/ml by using Chloramphenicol and Flucanazole as standards. These novel compounds was tested for antibacterial activity and found them to be effective against some gram positive and gram negative bacteria. One compound was found to be the most potent antimicrobial agent as compared with the standard drug [40].



(35)

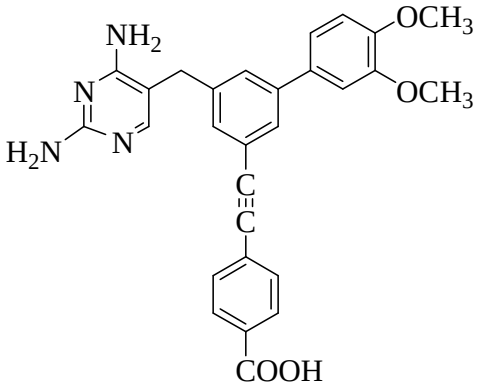
Pandeya *et al* synthesized 4-(4-chlorophenyl)-6-(4-methylphenyl)-2-aminopyrimidine compounds **(36)**. When compared to Trimethoprim, all compounds were active against bacterial stains like *Salmonella typhimurium*,

Staphylococcus aureus, *Enterococcus faecalis*, *P. aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus albus*, *Aeromonas hydrophila*, *Vibrio cholerae*, *Bacillus subtilis* and *Proteus rettgeri*. One of the tested compounds showed more potent activity (MIC=10 mg/ ml) than Sulphamethoxazole [41].



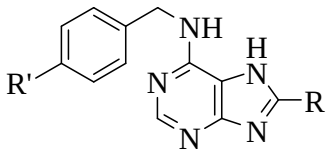
(36)

A series of 2,4-Diamino-5-[30,40-dimethoxy-50-(5-carboxy-1-pentynyl)]benzylpyrimidine and 2,4-diamino-5-[30,40-dimethoxy-50-(4-carboxyphenylethynyl)benzylpyrimidine derivatives **(37)** were synthesized by Forsch *et al* . The selectivity index (SI) for each compound was calculated by dividing its 50% inhibitory concentration (IC50). These novel analogues may be viewed as promising antimicrobial activity with respective to their reference drugs Gentamycin, Ampicillin and Norfloxacin [42].



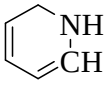
(37)

Tedder *et al* reported that structure-based design, synthesis, and biological activity of novel inhibitors of S-adenosyl homocysteine/methylthioadenosine (SAH/MTA) nucleosidase derivatives **(38)**. These compounds were active in antimicrobial assays, inhibiting the growth of three important pathogenic genera and showed promising antimicrobial activity with respective to their reference drug Ampicillin [43].

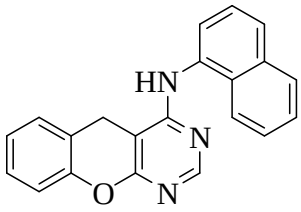


(38)

R = $(CH_2)_2C\text{-}C_5H_9$, R' = CO_2CH_3

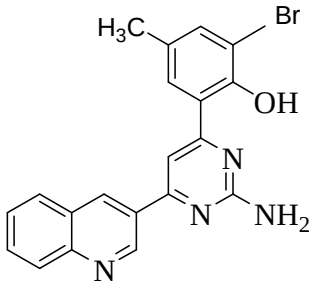
R = $(CH)_2C\text{-}C_5H_9$, R'= 

Rai *et al* synthesized novel chromeno pyrimidine to afford chromenopyrimidines derivatives **(39)**. All newly synthesized compounds were screened for antibacterial activity against all bacterial stains. These compounds showed excellent antibacterial activity at 1.6125 mg/mL concentration against *S. aureus* bacteria as compared to the standard drug Ceftriaxone. One compound showed potent activity as that of the standard which was active at 1.6125 mg/mL against bacterial stains *E. coli* and *P. aeruginosa*, *B. subtilis* [44].



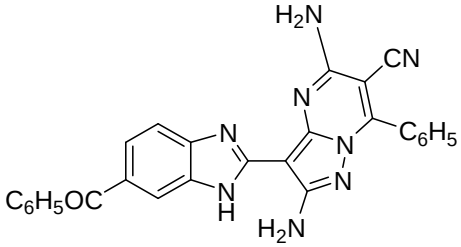
(39)

Dave *et al* reported a series of (E)-3-(2-chloroquinolin-3-yl)-1-(2-hydroxyphenyl) prop-2-en-1-one and its pyrimidine analogues e.g. 2-[2-amino-6-(2-chloroquinolin-3-yl)-5,6-dihydro pyrimidin -4-yl]phenols derivatives **(40)** . All the newly synthesized compounds were evaluated for their *in vitro* growth inhibitory activity against *Escherichia coli, Pseudomonas vulgaris, Bacillus subtilis, Staphylococcus aureus,Staphylococcus typhi, Candida albicans, Aspergillus niger* and *Pseudomonas chrysogenum*. Their zone of inhibition values were compared with the standard drugs Ampicillin and Amphotericin B and showed maximum inhibition of growth of microorganism at concentration of 200 ug/ml [45].



(40)

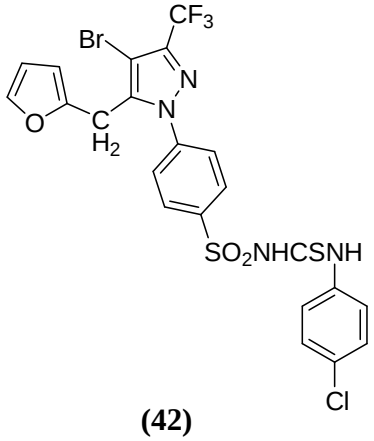
Pyrazolo pyrimidines derivatives **(41)** were synthesized by Zaharan *et al* via the reaction of ketene dithioacetals and 5-aminopyrazoles. Most of the synthesized compounds were found to possess various antimicrobial and antifungal activities with minimal inhibitory concentration (MIC) values ranging between 100–250 mg/ml. However, one of the tested compounds showed superior antimicrobial activity than the reference drug Ampicillin [46].



(41)

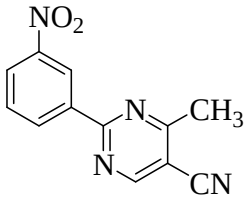
Faidallah *et al* introduced fluorinated pyrazoles and benzenesulfonylurea derivatives as well as their cyclic sulfonylthioureas derivatives **(42)**. Biological screening of prepared compound revealed significant antibacterial activities. All the compounds showed antimicrobial activities against *Escherichia coli*, *Staphylococcus aureus*,

Aspergillus niger and *Candida albicans*. Two compounds exhibited potent activities against various stains of micro-organisms in the comparison to reference drug Ciprofloxacin [47].



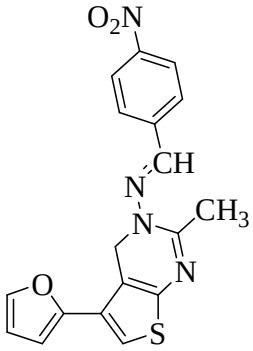
(42)

Petra *et al* reported some versatile 2-Ethoxymethylene-3-oxobutanenitrile pyrimidine derivatives **(43)** and found broad spectrum of antimicrobial activity which was effective against various bacteria *Bacillus subtilis*, *Staphylococcus aureus* and filamentous fungi *Aspergillus niger* and *S. aureus, A. niger* and *Staphylococcus aureus*. One compound manifested the highest antimicrobial activity which was most active as compared to Ampicillin and Amphotericin [48].



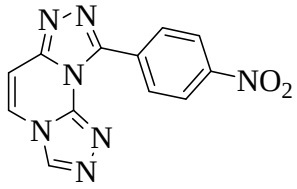
(43)

Two novel series of N-[5-(2-furanyl)-2-methyl-4-oxo-4*H*-thieno pyrimidin-3-yl]-carboxamide and 3-substituted-5-(2- furanyl)-2-methyl-3*H*-thieno pyrimidin-4-ones derivatives **(44)** were synthesized by Chambhare *et al*. All the compounds were assayed *in vitro* for antibacterial activity against two different stains of Gram-negative (*Escherichia coli and S. typhi)* and Gram-positive *(S. aureus , B. subtilis*) bacteria. In general, along with the thienopyrimidinone ring, substituted amido or imino side chain is essential for antimicrobial activity. One compound was found to be the most potent and found to be non-toxic up to a dose level of 200 mmol/L when compared with the standard drugs Ampicillin, Rifampin, Isoniazid, Penicillin and Chloramphenicol [49].



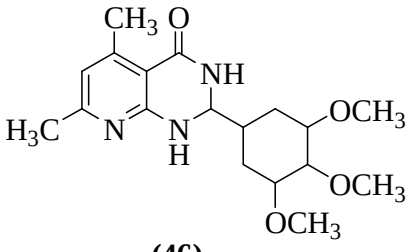
(44)

Prakash *et al* introduced three compounds, namely 3,9-di-(40-fluorophenyl)-bis-1,2,4-triazolo pyrimidine 3,9-di-(40-nitrophenyl)- bis-1,2,4-triazolo pyrimidine and 3,9-di-(50-nitro-20-furyl)-bis-1,2,4-triazolo pyrimidine derivatives **(45)** associated with substantially higher antibacterial activity than some commercial antibiotics against Gram-positive bacteria namely *Staphylococcus aureus*, *Staphylococcus epidermidis and Bacillus subtilis* and two Gram-negative bacteria namely *Salmonella typhi* and *Escherichia coli* at MIC (minimum inhibitory concentration) 10 mg/ml as compared with the reference drug Chloremphenicol [50].



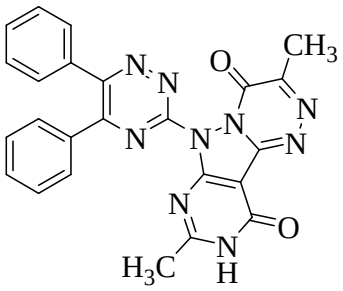
(45)

Narayana *et al* synthesized 2-Substituted-5,7-dimethyl pyrido pyrimidin-4(1*H*)-ones derivatives **(46)**. All compounds were screened for antibacterial activity against Gram positive and Gram negative bacteria. The synthesized compounds were screened for their *in vitro* antibacterial activity against Gram positive *(B. subtilis* and *S. aureus)* and Gram negative (*E. coli* and *K. pneumoniae)* bacteria. One compound was obtained containing antibacterial activity at minimum inhibitory concentration at 1.25 mg/ml and showed greater activity against all species of Gram positive and Gram negative bacteria compared to Ampicillin [51].



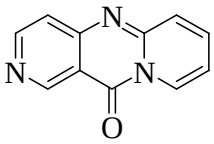
(46)

El-Sayed *et al* synthesized pyrazolo pyrimido pyrimidine derivatives **(47)**. The entire compounds were screened for their antibacterial and antifungal activities. The serial dilution technique was applied for the determination of MIC of the tested compounds against species of bacterial stains *E. coli*, *Staphylococcus aureus* (MTCCB), *Staphylococcus epidermidis* and *Escherichia coli* and species of fungal stains *A. niger, A. alternate, Aspergillus fumigatus, Aspergillus niger and Alternaria alternate.* One of the tested compounds showed superior antimicrobial activity than the reference drug Ampicillin [52].



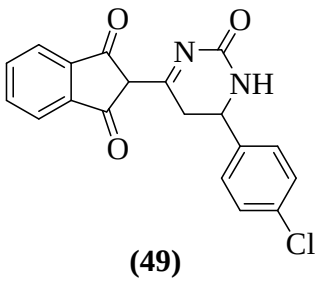
(47)

Ababsa *et al* reported Dipyrido pyrimidin-11-one and dipyrido pyrimidin-5-one derivatives **(48)** and evaluated for antimicrobial and antifungal activities. Dipyrido- pyrimidin-5-one and pyrido pyrimidino isoquinolin-8-one derivative showed good fungicidal activity against *Fusarium* and dipyrido pyrimidin-11-one derivative against *Candida albican Fusarium, Aspergillus niger*. One compound showed a excellent bactericidal activity against various bacteria (*Escherichia coli and Pseudomonas aeroginosa*), similar to that of Ciprofloxacin, against *Pseudomonas vaeroginosa*, and also showed a good fungicidal activity, similar to that of Nystatin, against *Fusarium* and against *Candida albicans*. One compound was found to have more promising activities compared to a reference drug Doxorubicin [53].



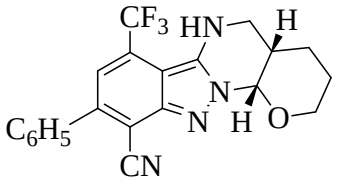
(48)

Giles *et al* reported that the indane-1,3-dione a new group of pyrimidine derivatives **(49)** aiming at the synthesis of new compounds having antimicrobial activity in a single component and evaluated for antimicrobial and antifungal activities. The chlorophenyl substituted pyrimidine derivatives exhibits good antifungal and antimicrobial agent against *Escherichia coli* and *Bacillus subtilis*. Some compounds showed good inhibition at 31.2 mg/mL against *Pseudomonas aeruginosa, Staphylococcus aureus, Aspergillus niger* and *Candida albicans*. Amongst this series, one compound showed good inhibition against all the tested bacterial and fungal stains as compared to standard drugs Ampicillin and Fluconazole [54].



(49)

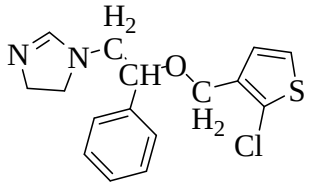
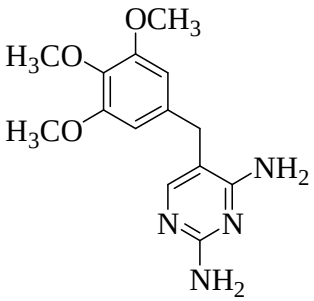
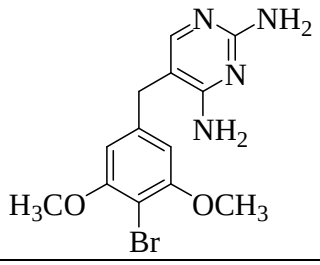
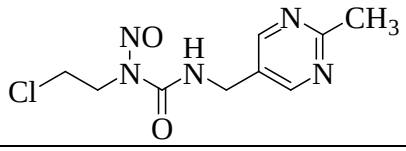
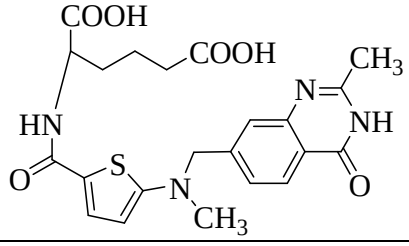
Yakaiah *et al* reported a series of 4,8-diphenyl-10-(trifluoromethyl)- 1,2,3,4-tetrahydropyrimido indazole-7-carbonitrile derivatives **(50)** which were evaluated for antibacterial activity. All the compounds showed significant activity against all species of Gram-positive (*B. subtilis, S. aureus*) and Gram-negative (*P. aeruginosa, E. coli*) bacteria *in vitro*. In conclusion, the MIC values of the tested compounds were compared with Penicillin and Streptomycin as standard drugs. Only one compound showed promising activity against yeast and filamentous fungi at maximum concentration of 150 mg/ml [55].

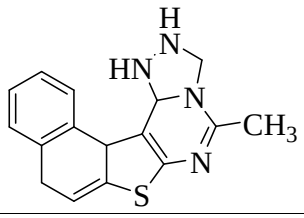
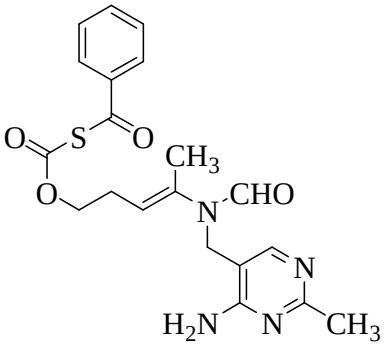
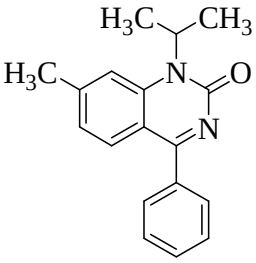
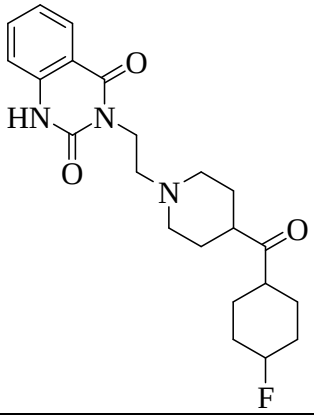
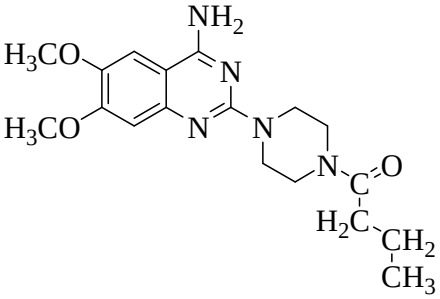


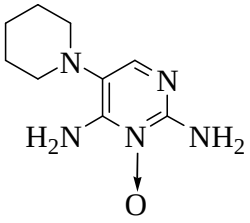
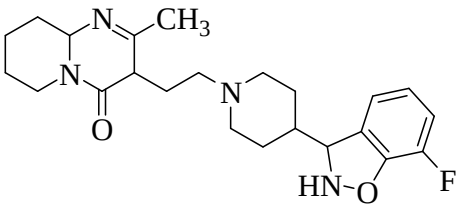
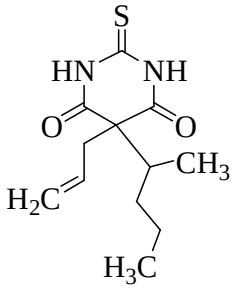
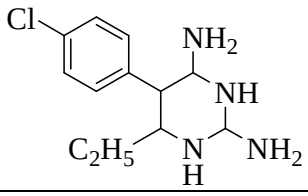
(50)

Some of the clinically used pryimidine based drugs have been enlisted in the table no. 1 as given below which indicates the importance of pyrimidine nucleus in modern clinical therapy.

Table No.1: Successful Pyrimidine Based Drugs Available in Clinical Therapy [56-74].

S. No.	Brand Name	Chemical Structure	Pharmacological Use
1.	Tioconazole®		Antifungal
2.	Trimethoprim®		Antibacterial
3.	Brodiprim®		Antibacterial
4.	Nimustine®		Antitumor
5.	Raltitrexed®		Antitumor

6.	Thienotriazolopyrimidine®		Anti-inflammatory
7.	Acetiamie®		Analgesic
8.	Proquazone®		Anti-inflammatory
9.	Ketanserin®		Antihypertensive
10.	Trimazosin®		Antihypertensive
11.	Minoxidil®		Antihypertensive

			
12.	Risoperidone®		Antipsychotic
13.	Thimylal®		General Anaesthetic
14.	Pyrimethamine®		Antimalarial

CONCLUSION

Microbial diseases are accountable for increasing the global mortality rates every year as per reports of WHO therefore innovation and advancement of effective antimicrobial drugs with novel modes of action has become a great concern for medicinal chemists working in this field. Pyrimidine derivatives play an imperative role in the pharmaceutical field because they possess competent antimicrobial biological activities. This manuscript is an endeavor to report the antimicrobial activities of novel pyrimidine derivatives during recent years with a mission to resolve the global problem of microbial resistance towards antibiotics and to develop efficient antimicrobial agents.

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