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Review Article

RECENT ADVANCES IN ANTIMICROBIAL ACTIVITY OF PYRIMIDINES: A REVIEW

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ABSTRACT

Over the past era, development of small heterocycles as potential therapeutics has been a zone of major interest. A large number of pyrimidine derivatives are of considerable biological and chemical interest. Pyrimidine derivatives have shown numerous biological activities such as antimicrobial, antitubercular, anticancer, anticonvulsant, antidiabetic, antiviral, and anti-inflammatory. Being a heterocyclic compound, Pyrimidine finds its use for designing synthesis of newer biologically active structures, as its aromaticity makes it relatively stable, also reactive sites which allow for functionalization. Several amino derivatives of nitrogen-containing heterocycles such as pyrimidine, pyridine possess an antimicrobial activity. In this review, recent advancements in the antimicrobial activity of pyrimidine derivatives have been reported.

Keywords: Pyrimidine, Antimicrobial, Antibacterial, Antifungal.

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INTRODUCTION

Pyrimidine is the most important six-membered aromatic heterocyclic ring containing two nitrogen atoms. The replacement of C-H units meta to each other in a benzene ring by two nitrogen atoms gives pyrimidine. The reactivities of 2,4,5 and 6 carbon atoms, as well as substituents attached to them, vary individually. Although the parent compound, pyrimidine is not widely used, many of its derivatives are found in commercial products or in nature [1-3] (Fig. 1).

In the past several decades there has been a significant increase in the preparation of pyrimidine derivatives and their biological activity. Many substituted pyrimidines have been reported to display a large panel of biochemical properties, including anticonvulsant, antibacterial, antitumor, antiviral, and antibiotic activities [4]. Variation of substituents on the pyrimidine nuclei could potentially affect the interaction of the molecules with biological targets. The wide range of biological activity and versatile synthetic applicability of these heterocyclic compounds will help the medicinal chemists to plan, organize and implement new approaches toward discovery of novel drugs. Thus, pyrimidine compounds received much attention from medicinal as well as synthetic organic chemists [5,6].

STRUCTURE ACTIVITY RELATIONSHIP OF PYRIMIDINES (FIG. 2)

- As SAR studies give insights into the molecular properties causing receptor affinity and selectivity, The promising nature of compounds may be attributed to the substitutions at the hydrophobic domain.
- These compounds had electron-withdrawing and donating groups at the ortho, meta, and para position of the hydrophobic aryl ring. In overall, it was noticed that the substituted derivatives have more activity than the other derivatives.
- This may be because of the fact that substituted derivatives are better fitted into the receptor site.

Position A

Substitution at five-membered saturated heterocyclic ring leads to anticancer and antiviral activities.

Position B

i. Substitution at 2nd position with five or six-membered saturated heterocyclic ring directs to anthelmintic, antiparkinsonian, expectorant activity, and treatment of GI disturbance.

ii. 2nd and 4th position keto group substitution or amino substitution or mixed keto, amino groups substitution leads to anticancer, antiviral, antibacterial, antifungal, and treatment of respiratory tract infection and liver disorder.

Position C

Substitution at 5th position with substituted amine or saturated distal heterocyclic ring or halogen leads to antibacterial and anticancer activities.

Position D

Fifth and 6th position fused with other heterocyclic ring and *o*, *m*, *p* substituted with aryl ring. This substitution leads to anticancer antiviral, antibacterial, vasodilation, and treatment of UTI [5,7-11].

RECENT ADVANCES IN ANTIMICROBIAL ACTIVITY OF PYRIMIDINE DERIVATIVES

Abd El-Aleam *et al.* synthesized a series of 1,2,4-triazolo[1,5-a] pyrimidine derivatives and screened for their antibacterial and antifungal activities as well as their safety profile. Synthesized compounds were evaluated for their antibacterial activity against five bacterial strains: *E. coli*, *K. pneumoniae, A. baumannii, P. aeruginosa* (Gram negative), and Methicillin-Resistant *S. aureus* (MRSA) (Gram-positive) using ciprofloxacin as a positive control. The antifungal activity screening against two fungal species, *C. albicans,* and *C. neoformans*, was performed using fluconazole as a positive control. Furthermore, compounds displaying significant growth inhibition % (80–100%) at 32 μg/mL against any of the tested bacterial or fungal species were screened for their minimum inhibitory concentrations (MIC). Among the synthesized compounds both benzohydrazide derivatives **1** (Fig. 3) exerted high activity against the tested bacterial strains with MIC values 0.25–1 μg/mL [12].Panneerselvam and J R Mandhadi synthesized new series of antimicrobial thiosemicarbazide substituted pyrimidine derivatives by using thiosemicarbazide and ethyl 2-((2-amino-5-carbamoyl-6-[substituted benzyl] pyrimidin-4-yl)oxy)acetate derivatives and subsequent addition of acetaldehyde and acetone. The designed compounds were screened for antibacterial activity against *Staphylococcus aureus, Staphylococcus epidermidis, Micrococcus luteus, Bacillus cereus, Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumonia* in comparison with the standard drugs Ciprofloxacin and antifungal effect against *Aspergillus niger* and *Aspergillus fumigates* in comparison with the standard drug Ketoconazole. In accordance

with the data obtained from antimicrobial activity, all the synthesized derivatives have shown good activity against the tested microbes. Among them, compound bearing 2-hydroxy and 3-chloro derivatives of thiosemicarbazide substituted pyrimidine **2** (Fig. 4) has shown good activity against all the tested organisms [13]. AlNeyadi *et al*. designed and synthesized a series of pyrimidine derivatives and evaluated their antimicrobial activity. Among them, compound 3 exhibited the best activity with the MIC values of 1.0 μg/ml against *E. coli* and *Pseudomonas aeruginosa*. Then, the antimicrobial activity of compound

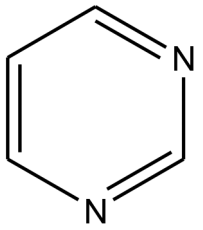


Fig. 1: Pyrimidine nucleus

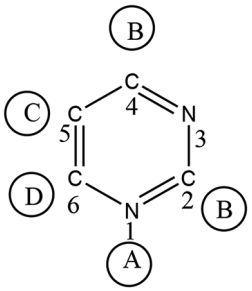


Fig 2: Positions for substitution on pyrimidine ring

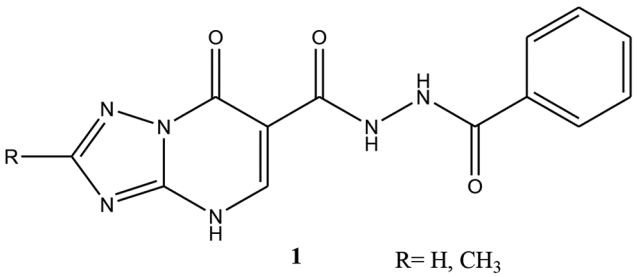


Fig. 3: 1,2,4-triazolo[1,5-a] pyrimidine derivatives

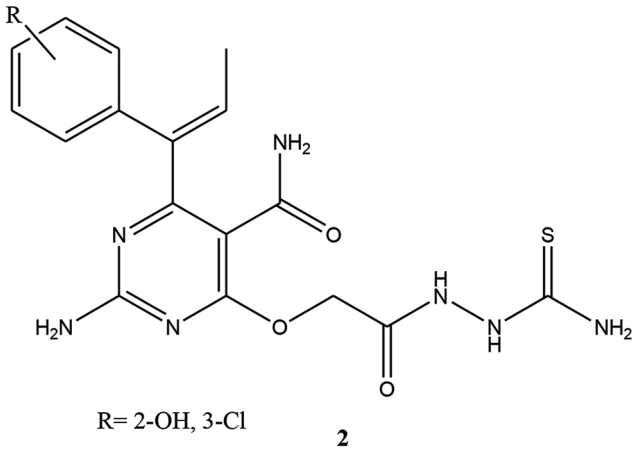


Fig. 4: Thiosemicarbazide substituted pyrimidine derivatives

3 (Fig. 5) combined with amoxicillin was also been tested. Docking studies revealed that the formation of the covalent complex suggested that the enzyme would be permanently damaged, resulting in cell wall synthesis inhibition. Indeed, further work is required to confirm that the PBP enzyme is a target for our novel antibacterial agents [14].

Mantipally *et al.* designed and synthesized novel homopiperazine linked imidazo[1,2-a] pyrimidine derivatives. Synthesized compounds were also evaluated for their antimicrobial activity by cup plate diffusion method. Some of the synthesized compounds displayed remarkable antimicrobial activity relating to their standard drugs Gentamycin, Amphotericin B, and Ampicillin. Significantly, compound with the -$N(Me)_2$ group was introduced on the homopiperazine 4 (Fig. 6) unit showed broad-spectrum activity against tested microbial strains [15].

The utility of the enaminonitriles for the synthesis of the pyrazole derivatives, diaminopyrimidine derivatives, pyrazolo[1,5-a] pyrimidines, triazolo[4,3-a] pyrimidines, and imidazo[1,2-a] pyrimidine derivatives was explored by A M farag and A M Fahim. The synthesized compounds were examined for antimicrobial strains. The most active compound was found to be **5** and compound **6** (Fig. 7) showed one of the highest observed activities against *B. subtilis* and *Geotricum candidum*. The increased antimicrobial activity might be due to the carboxyl group [16].

Shehab *et al*. synthesized series of pyrimidines and condensed pyrimidine derivatives. Antimicrobial activity of the prepared compounds was investigated against different bacterial and fungal species, such as *E. Coli* ATCC11229, *listeria* ATCC8729, *S. aureus* ATCC6538, *Salmonella typhi* ATCC14028, and *Aspergillus niger* OC10. The oxazolopyrimidine derivative **7** (Fig. 8) showed the highest antibacterial activity [17].

Al-Bogami *et al.* synthesized a series of novel fused pyrimidine derivatives possessing a trifluoromethyl moiety by the reaction of the enaminone named E-3-(dimethylamino)1-(4-(trifluoromethyl) phenyl) prop-2-en-1-one with a variety of heterocyclic amines under solvent-free mechanochemical condition utilizing nano-sized magnesium oxide catalyst. The newly

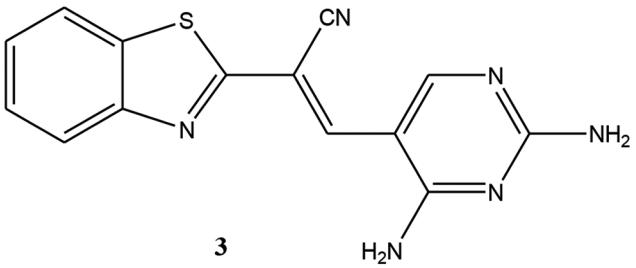


Fig. 5: Benzazole acrylonitrile-based pyrimidine derivatives

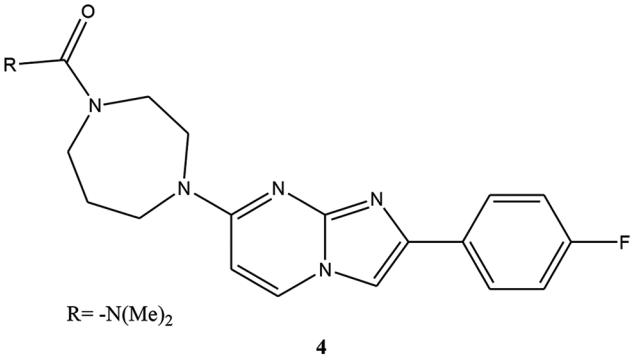
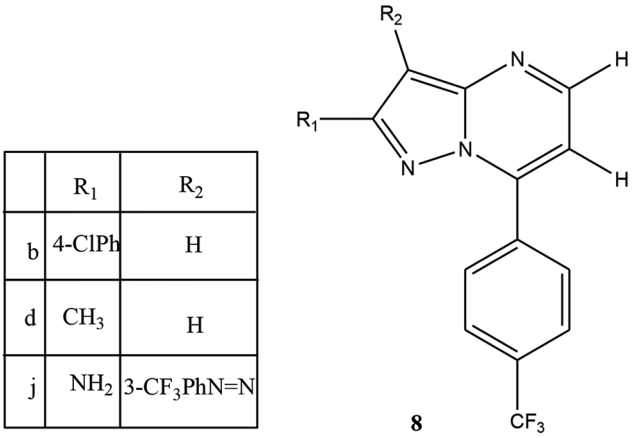


Fig. 6: Homopiperazine linked imidazo[1,2-a] pyrimidine derivatives

synthesized compounds were evaluated for their in vitro antibacterial activity against *Escherichia coli* (ATCC25922) and *Pseudomonas aeruginosa* (ATCC27953) as examples of Gram-negative bacteria and *Staphylococcus aureus* (ATCC29213) and *Bacillus subtilis* (NRRL-B-4219) as examples of Gram-positive bacteria. They were also evaluated for their in vitro antifungal potential against a representative panel of fungal strains, i.e., *Candida albicans* (ATCC10231). Compound 8b exhibited broad spectrum and remarkable antimicrobial activity, Moreover, 8d and 8j (Fig. 9) showed good antimicrobial efficacy toward the tested organisms [18].

Dofe *et al*. developed convenient and facile methodology for the synthesis of new series of pyrazole and pyrimidine derivatives under ultrasound irradiation. The synthesized compounds were screened for their antimicrobial activity against four bacteria (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa*) and two fungi (*Candida albicans, Aspergillus niger*). Among the synthesized compound, one without substituent, having dichloro substituent, and with chloro, methyl substituent (Fig. 10) exhibited potent activity, indicated that compounds with electron-donating groups are responsible for the enhanced activity of the compounds [19].

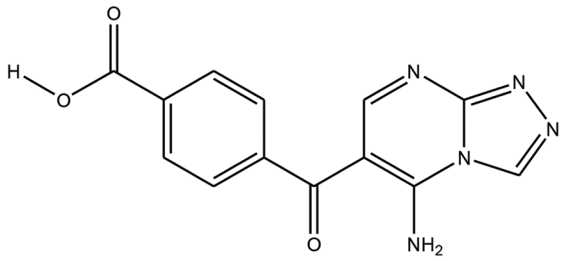
Veeraswamy *et al*. prepared a series of novel pyrido[2,3-d] pyrimidine derivatives starting from 2-amino-3-cyano-4-trifluoromethyl-6-phenyl pyridine via Grignard's reaction, cyclization followed by coupling with aliphatic and cyclic amines. All the compounds were screened for antibacterial, minimum bactericidal concentration (MBC), as well



	R_1	R_2
b	4-ClPh	H
d	CH_3	H
j	NH_2	3-CF_3PhN=N

8

Fig. 9: Fused pyrimidine derivatives possessing a trifluoromethyl moiety



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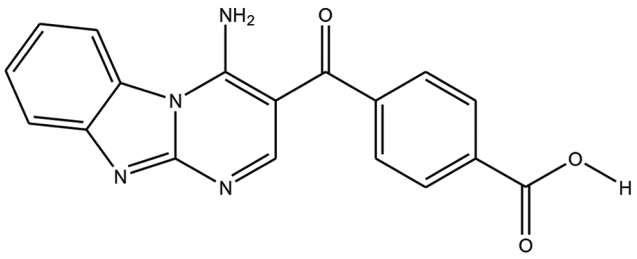

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Fig. 7: Triazolo[4,3-a] pyrimidines and imidazo[1,2-a] pyrimidine derivatives

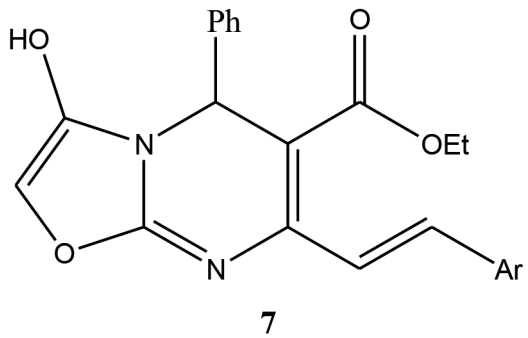

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Fig. 8: Oxazole condensed pyrimidine derivatives

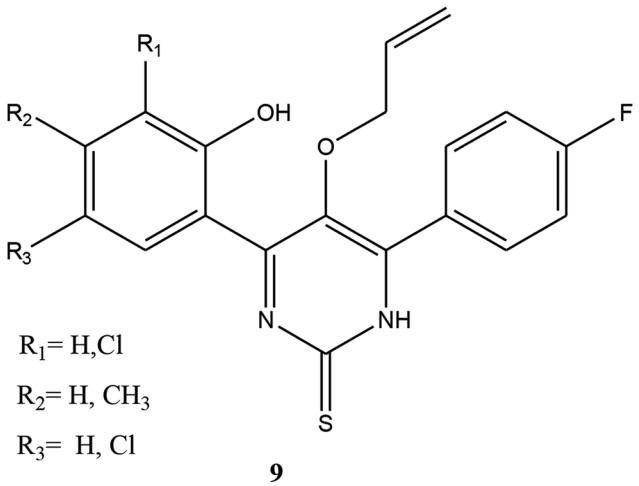

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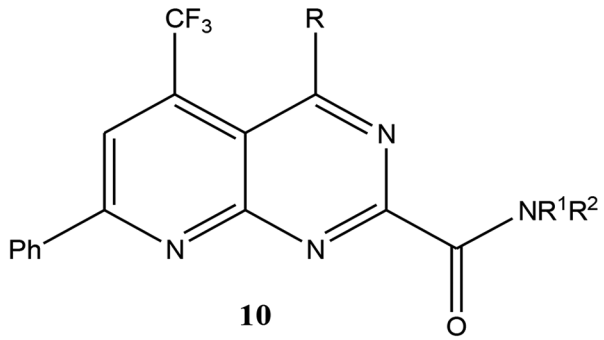
Fig. 10: Thiopyrimidine derivatives



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R= C_6H_5, 4-$MeOC_6H_5$

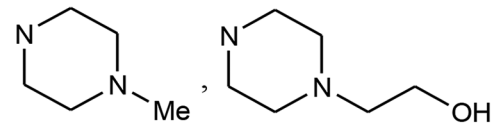
NR^1R^2 = 

Fig. 11: Pyrido[2,3-d] pyrimidine derivatives

as antifungal and minimum fungicidal concentration (MFC) activities. Among the screened compounds, **10** (Fig. 11) exhibiting promising activity have been identified. The results reveal that the compound pyrido[2,3-d] pyrimidine derivative altered the sterol profile which may exert its antifungal activity through inhibition of ergosterol biosynthesis and could be an ideal candidate for antifungal therapy [20].

Mohamed *et al*. designed and synthesized new pyrimidine derivatives. Some of the newly synthesized compounds were assayed in vitro for their antimicrobial activity against two gram-negative bacteria: namely, *Pseudomonas aeruginosa* and *Escherichia coli*, and two gram-positive bacteria: *Staphylococcus aureus* and *Bacillis subtilis* and two fungal species, namely: *Aspergillus flavus* and *Candida albicans*. The fungicide Colitrimazole and the bactericides Ampicillin were used as references to evaluate the potency of the tested compounds under the same conditions. Hydrazino derivative (11) and acetohydrazide derivative 12 (Fig. 12) were found to have pronounced inhibition effect [21].

Andrews *et al*. synthesized and compared the antibacterial activities of pyrimidine derivatives. The newly synthesized pyrimidine derivatives were screened for their antibacterial activity in vitro against *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Escherichia coli*, using agar well disk diffusion method. Among the synthesized derivatives, triazole substituted compounds 13 (Fig. 13) have shown higher antibacterial inhibition when compared to the thiadiazole derivatives [22].

Khalifa *et al*. synthesized a series of novel substituted thioxopyrimidine and thiazolo[3,2-a] pyrimidine compounds (Fig. 14) that combine various heteroaryl rings via Biginelli one-pot three-component reaction. Antibacterial activity was tested against several bacterial strains isolated from food of animal origin: one pathogenic Gram +ve bacteria stain, *Staphylococcus aureus,* and two pathogenic Gram –ve bacteria stains, *Salmonella typhimurium,* and *Pseudomonas aeruginosa*. For antifungal activity, *Candida albicans* and *Aspergillus flavus* were utilized [23].

Okasha *et al*. synthesized new series of chromeno pyrimidine derivatives. All the newly synthesized compounds were screened for their in vitro antimicrobial activity at 25 μg/mL to determine the zone of inhibition against four Gram-positive bacteria: *Staphylococcus aureus* (RCMB 000106), *Staphylococcus epidermidis* (RCMB 000107), *Bacillus subtilis* (RCMB 000108), *Bacillus pumilus* (RCMB 000109), and two Gram-negative pathogenic bacteria: *Pseudomonas aeruginosa* (RCMB 000102), *Escherichia coli* (RCMB 000103) using two standard antibiotics (ampicillin, streptomycin) as reference drugs, and three fungi: *Aspergillus fumigatus* (RCMB 002003), *Candida albicans* (RCMB 005002) and *Saccharomyces cerevisiae* (RCMB 006002) using two standard antibiotics (mycostatine, clotrimazole) as reference drugs. It was demonstrated that 7H-benzochromenopyrimidine (15) and

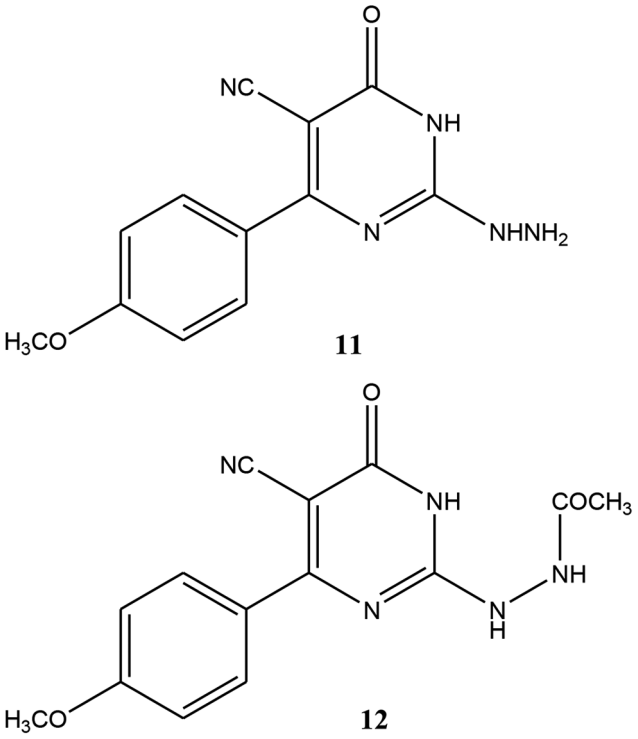


Fig. 12: Hydrazino pyrimidine derivative

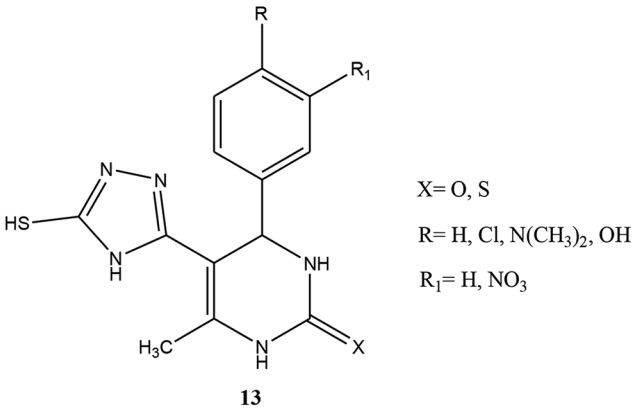


Fig. 13: Triazole substituted pyrimidines

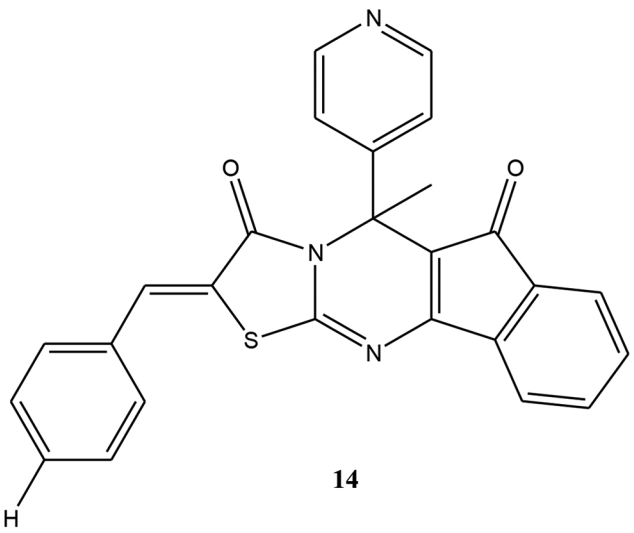


Fig. 14: Thiazolo[3,2-a] pyrimidine compounds

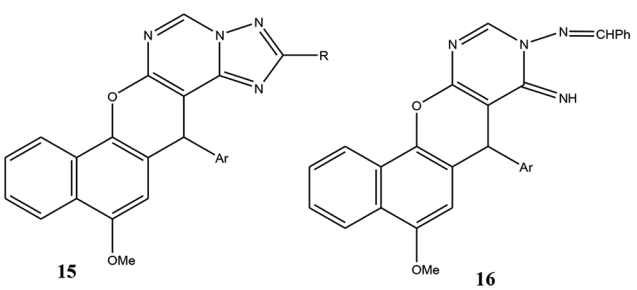


Fig. 15: Chromeno pyrimidine derivatives

derivatives of 14H-benzochromenotriazolopyrimidine 16 (Fig. 15) exhibited the most promising antibacterial activities compared to the reference antimicrobial agents [24].

Virupakshi *et al.* have reported the design, synthesis, characterization & biological activity of novel thieno [2,3-d] pyrimidine derivatives. The final compounds were screened for their antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* from the Gram-positive group of bacteria. *Pseudomonas aeruginosa* and *Escherichia coli* from Gram-negative group of bacteria. Antifungal activity against *Aspergillus niger* and *Candida albicans*. The structure and biological activity relationship of title compounds indicate that the presence of electron-withdrawing groups such as - CF_3 and -OCF_3 attached to the phenyl ring and thiophene, Furan rings (Fig. 16) were responsible for good antimicrobial activity [25].

Al- Juboori and Mahmood have reported Synthesis, antimicrobial evaluation, density functional theory, and docking studies of some new 2-mercapto pyrimidine Schiff bases to display antimicrobial activity and antifungal activities. The synthesized derivatives were screened for their in vitro, antibacterial activity against two Gram-positive bacteria: *Bacillus subtilis* and *Staphylococcus aureus* and Gram-negative bacteria: *Klebsiella pneumoniae, Escherichia coli*, and *Salmonella typhi*, and the results showed that most of them have good antibacterial activity. While their antifungal activity against four fungi species (*Aspergillus fumigates, Aspergillus niger, Aspergillus terrus,* and *Rhizopus*). Results obtained from molecular docking discovered that compounds with bulky phenyl groups (Fig. 17) are important for blocking the active centers of glucose -6-phosphate synthase in bacteria and fungi [26].

Khatri and Shah reported the effective microwave synthesis of bioactive Thieno [2,3-*d*] pyrimidines. All of the synthesized compounds were tested for their antibacterial and antifungal activity (MIC) *in vitro* using two Gram-positive bacteria *Staphylococcus aureus*, *Streptococcus pyogenes*, two Gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa,* and three fungal strains *Candida albicans*, *Aspergillus niger*, *Aspergillus clavatus.* The compound (Fig. 18) was found to be exhibited significant antimicrobial activity [27].

Triloknadh *et al*. synthesized a series of thieno[2,3-d] pyrimidine alkyne Mannich base derivatives and thieno[2,3-d]pyrimidine 1,3,4-oxadiazole derivatives. All of the synthesized compounds were screened for their antibacterial activity against the four bacterial strains such as *S. aureus, B. subtilis, E. coli*, and *P. aeruginosa* on par with reference drug gentamicin. Structure activity relationship studies (SAR) revealed the change in the substitutions on the C4 position of thienopyridine ring and terminal phenyl ring (Fig. 19) leads to substantial changes in the biological activities [28].

Gupta *et al*. reported the synthesis of new pyrimidine-based derivatives and evaluated their antimicrobial activity against four different strains, viz two Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*) and two Gram-negative bacteria (*Escherichia*

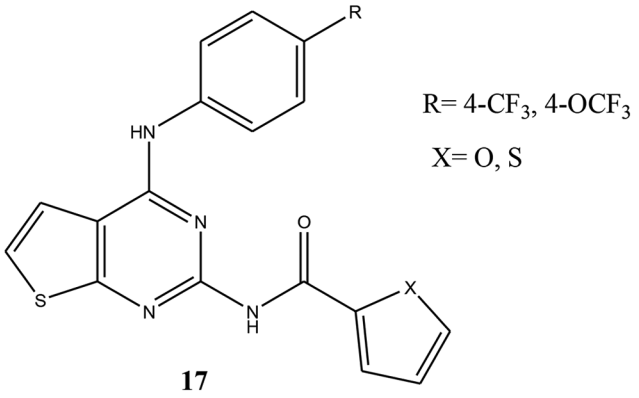


Fig. 16: Furan substituted thieno [2,3-d] pyrimidines

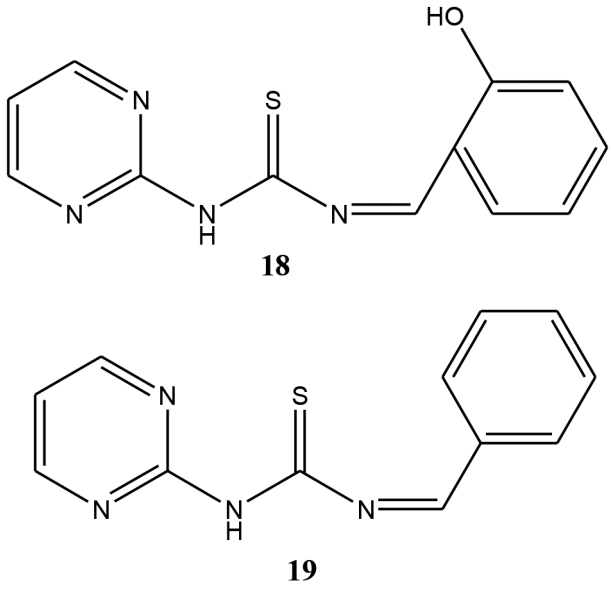


Fig. 17: 2-mercapto pyrimidine Schiff bases

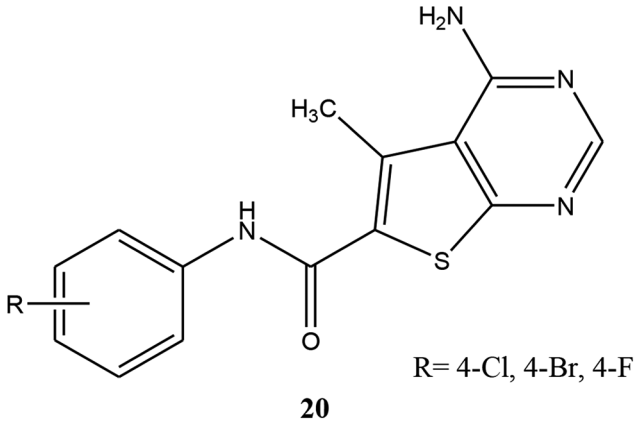


Fig. 18: Thieno [2,3-d] pyrimidines

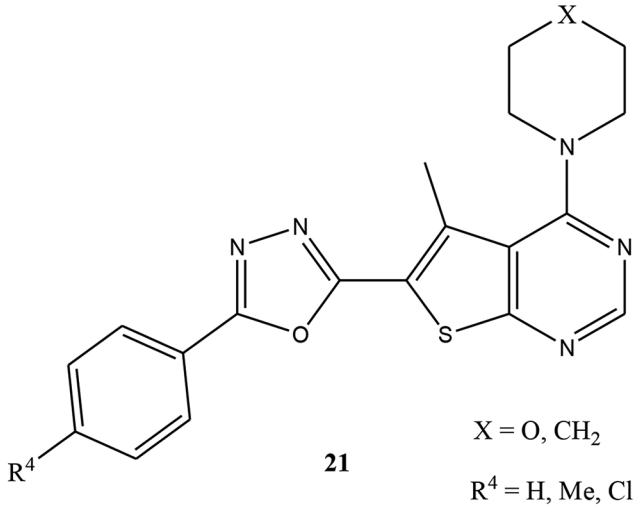


Fig. 19: Thieno[2,3- d]pyrimidine 1,3,4-oxadiazole derivatives

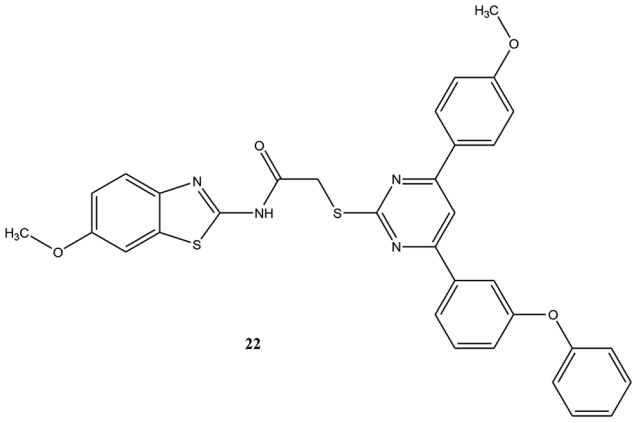


Fig. 20: Pyrimidine based derivatives

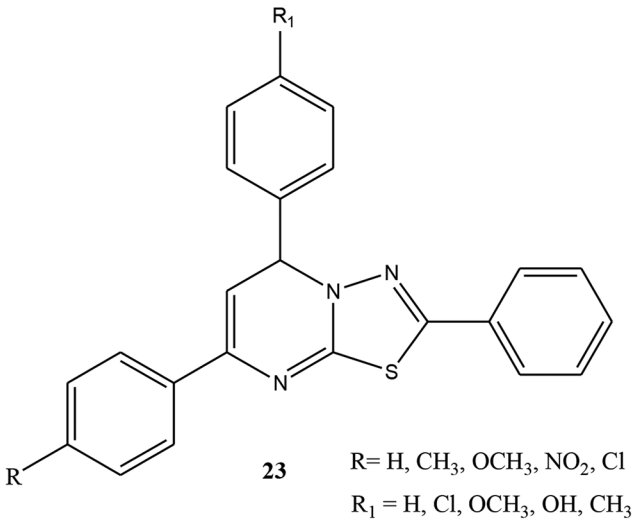


Fig. 21: 5,7-disubstituted-2-phenyl-5H-[1,3,4] thiadiazolo[3,2-a] pyrimidines

coli & *Pseudomonas aeruginosa*), analyzed with standard drugs ampicillin, chloramphenicol, ciprofloxacin, & norfloxacin. Antifungal activity was screened against *Candida albicans*, and *Aspergillus niger* organisms analyzed with standard drugs nystatin and griseofulvin. Some of the compounds **22** (Fig. 20) were effective as antimicrobial and antifungal agents [29].

Venkatesh *et al*. reported the synthesis of a series of 5,7-disubstituted-2-phenyl-5H-[1,3,4] thiadiazolo[3,2-a]pyrimidine derivatives. The title compounds were synthesized by the reaction of substituted chalcones with 5-phenyl-1,3,4-thiadiazol-2-amine in n-butanol. Anti-microbial activity of the synthesized compounds was tested against seven microbial strains (*Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Shigella* sp*, Candida albicans, Aspergillus niger, Alternaria alternate*) using the agar well diffusion method. The compounds (Fig. 21) displayed significant antimicrobial and antioxidant activities [30].

Madawali *et al.* synthesized a new series of pyrimidines of 6-chlorobenzimidazoles by the reaction of chalcone derivatives of 6-chlorobenzimidazole with guanidine nitrate in ethanol and aqueous solution of sodium hydroxide. The synthesized products have been tested for antibacterial activity against two Gram-positive bacteria viz., *Bacillus subtilis, Staphylococcus aureus*, and two Gram-negative bacteria viz., *Proteus mirabilis* and *Escherichia coli*. The antifungal activity of the products has been screened against two fungi viz., *Aspergillus niger* and *Candida albicans* by cup plate method. Many of these products (Fig. 22) showed significant activity [31].

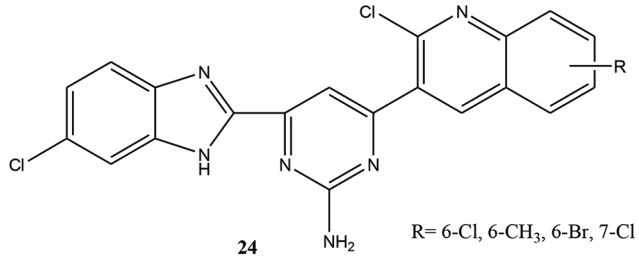


Fig. 22: Pyrimidines of 6-chlorobenzimidazoles

CONCLUSION

The literature reveals that compounds having pyrimidine nucleus possesses broad range of biological activities. Antimicrobial activity was significantly affected by slight change in substitution of pyrimidine rings. Substitutions at specific positions markedly enhance the activity. Hence, these findings will guide researchers to design and synthesize target compounds having pyrimidine nucleus with the hope that they may possess good antimicrobial activity.

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AUTHORS' CONTRIBUTIONS

Both authors contributed equally to writing the manuscript, analyzing the data, read and approved the manuscript.

CONFLICT OF INTEREST

None.

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