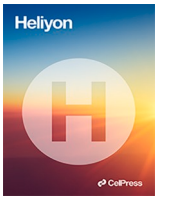
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Review article



Recent medicinal approaches of novel pyrimidine analogs: A review

Sharanabasappa B. Patil

Department of Chemistry, Ramaiah Institute of Technology, Bangalore, 560 054, India

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ABSTRACT

Pyrimidine derivatives attract researchers due to their versatile scaffold & their medicinal significance. Pyrimidine associated analogs are majorly contributed to the field of medicinal chemistry. In this review article, the recent new structural design and development of active agent studies and biological approaches are highlighted. In addition, the biological potency and the structure-activity relationship of pyrimidines such as antimicrobial, anticancer, anti-inflammatory, analgesic, anti-diabetic, anti-HIV, anthelmintic, CNS depressants, and cardiac agents are discussed. Finally, this review article may attract the researchers for new structural design and development of novel active pyrimidine scaffolds with more active and less harmful.

1. Introduction

Pyrimidine and its derivatives exhibited several therapeutic applications [1] which include antimicrobial [2], anticancer [3], anti-inflammatory [4], anti-malarial [5], anti-diabetic [6], anti- HIV [7], anthelmintic [8], CNS depressants [9], cardiac agents [10] and the thiouracil derivatives possess anti-thyroid activity [11]. In addition, fused pyrimidines have inhibitor activity against protein kinase [12]. Based on the above medicinal applications in this review manuscript the recent medicinal applications and structure activity relationship of pyrimidine associated analogs are discussed from the period of 2017 to 2021.

2. Medicinal approaches of pyrimidine analogs

2.1. As antimicrobial agent

Antibiotics are majorly contributing to human health globally. Multidrug resistance is a key challenge & some time improper usage of drug bacteria to gain a high resistance to antibiotics [13]. To overcome this issue a new structural design and development of novel active analogs with less resistance are needed [14].

Wenneng Wu et al. 2021 synthesized novel pyrimidine analogs & evaluated for antimicrobial activity. Among them, compound (**1**) exhibited higher potential (EC50: 10.5 μg/mL) against fungal strain (*B. dothidea, Phomopsis* sp. *& B. cinereal*) compared with standard (Pyrimethanil, 32.1 μg/mL). The enhanced activity is due to the presence of amine, fluorine, and bromine group at the 3rd, 2nd & 5th positions of the aromatic ring [**1**].

Xue Qian Bai et al. 2019. developed novel pyrimidine analogs & tested them for antimicrobial activity. Among which compound (**2**) exhibited satisfactory potential (MIC: 2.4 μmol/L) against used strains (*S. aureus, E. coli, and the F. Candida albicans*) compared with

E-mail address: sbp7910@gmail.com.

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standard. The observed potency may be due to the presence of benzyloxy-benzaldehyde moiety and pyrimidine scaffold [15].

Bassyouni F et al. 2021 synthesized novel fused pyrimidine analogs & evaluated for antimicrobial activity. Among all compounds (**3**) and (**4**) exhibited good potential against the bacterial and fungal strains (MIC: 10–17, 5 μL, *Bacillus cereus, E. coli, Pseudomonas aeruginosa, and Salmonella typhimurium and Rhizopus oligosporus & Candida albicans*) compared with standard. The enhanced activity may be due to the presence of methyl, amine and sulfur substituted pyrimidine moiety (Fig. 1) [10].

Mostafa et al. 2020 prepared new thienopyridine analogs & tested for antimicrobial activity. Among all compounds (**5**) showed prominent antimicrobial potential (Inhibition zone: 19, 19, 18 and 17 & 17, 18 & 18 mm) against (*Bacillus cereus, S. aureus, P. aeruginosa, and E. coli*) and (*C. Albicans, Trichophyton rubrum, A. favus*) compared with standard (Inhibition zone: 26, 25 & 21 mm). The observed activity may be due to the presence of substituted pyridine and pyrimidine scaffold [16]. Dofe Vidya S et al. 2018. developed new pyrimidine analogs & tested them for antimicrobial activity. Among them, compound (**6**) exhibited satisfactory potency against the bacterial strains (MIC: 25, 200, 175 & 150 μg/mL, *S. aureus, B. subtilis, E. coli & P. aeruginosa*) and fungal strains (MIC: 75 and 25 μg/mL, *Candida albicans & Aspergillus niger*) compared with standards (chloramphenicol and clotrimazole). The enhanced activity may due to the presence of fluorophenyl and thione-pyrimidine scaffold [17].

Moustafa A H et al. 2020 synthesized novel pyrimidine derivatives & tested for antimicrobial activity. Among the compounds (**7**) and (**8**) showed good potency against *S. aureus* (MIC 0.07 μg/mL) compared with the standard (MIC: 0.67 μg/mL). The observed activity may be due to the presence of hydroxyl, chloro-phenyl ring & pyrimidine scaffold (Fig. 2) [18].

2.2. As anti-cancer agent

Pyrimidine and its derivatives majorly contributed to the process of prevention and treatment of cancer. Cancer treatments (Chemotherapy and radiotherapy) have been associated with many side effects which affect the healthy human life and some therapies give even serious problems. According to a WHO report eighteen million people are presently affected with cancer and nine million people died from cancer in 2018 mainly due to less effective treatments [19].

Zuhal Kilic Kurt et al. 2020. developed new pyrimidine containing aryl urea analogs & evaluated for anticancer potential. Among all the compounds (**9**) and (**10**) exhibited satisfactory anticancer potency against colon and prostate cancer cell lines (IC_{50}: 11.08 μM, SW480). The enhanced activity is due to the presence of CF3, Cl, and amino-pyrimidine scaffold [20].

Huang T et al. 2019 synthesized novel pyrimidine analogs & tested for anticancer activity. Among the compounds (**11**) and (**12**) exhibits good anticancer potency against cancer cell lines (Inhibition rates: HeLa & A549: 45.08% & 41.69%) & (HeLa, HepG-2 & MCF7, IC_{50}: 20.30, 12.37 & 13.18 μM). The observed activity may be due to the presence of ethanolamine and pyrimidine moiety (Fig-3) [21].

Ahmed N M et al. 2021. developed new indolyl-pyrimidine hybrids and screened for anticancer potential. Among them, the compounds (**13**), (**14**) and (**15**) exhibited good anticancer activity against cancer cell lines (IC_{50}: 5.1, 5.02, and 6.6 μM, HepG-2, HCT-116, and MCF-7). The enhanced activity may be due to the presence of lipophilic substituent to phenyl ring on either the pyrimidine or thiazolidine scaffold [22].

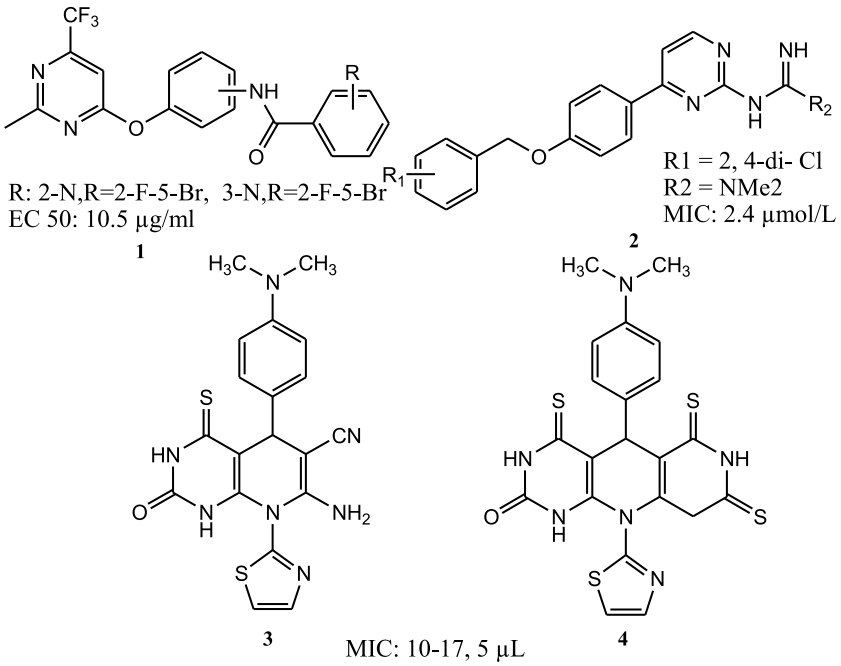


Fig. 1. Molecular structures of pyrimidine with antimicrobial potential.

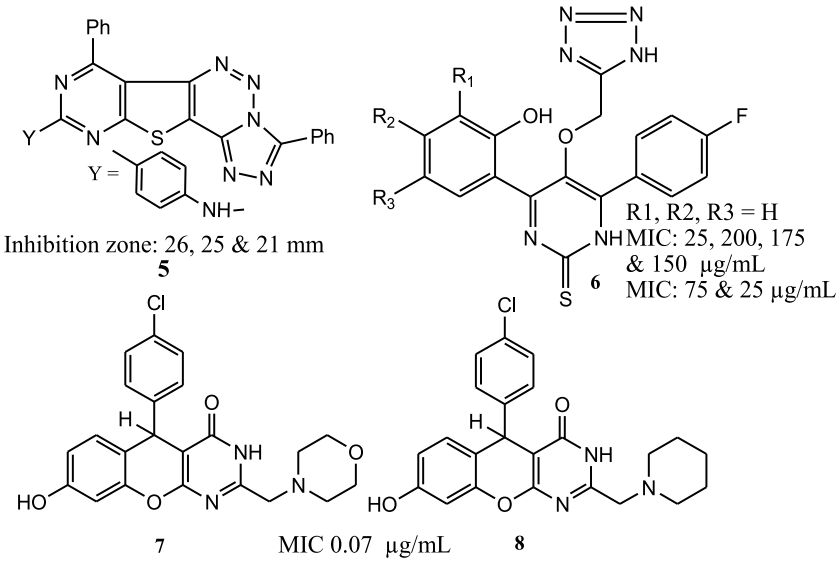


Fig. 2. Molecular structures of pyrimidine with antimicrobial potential.

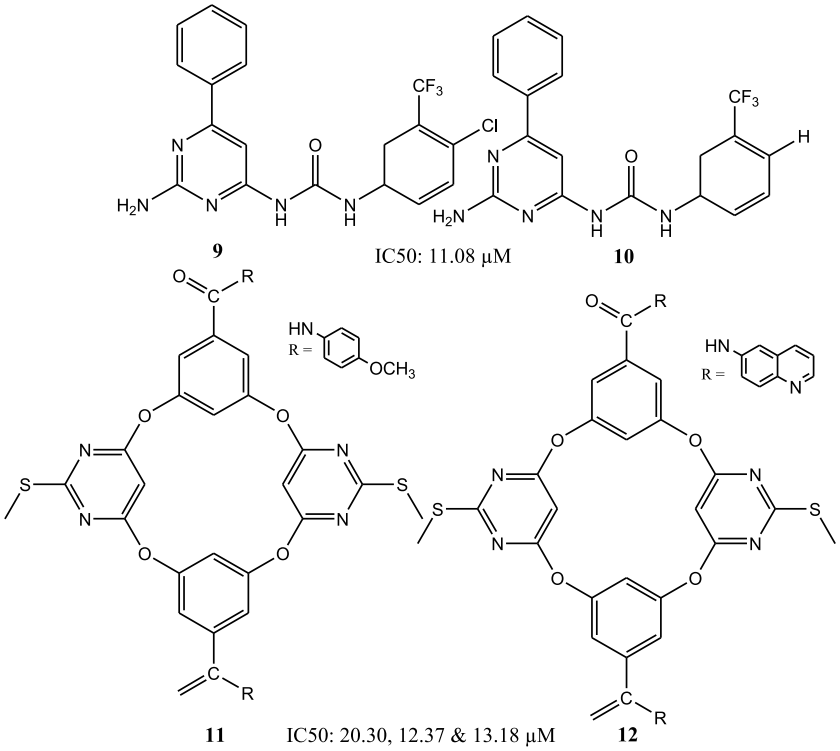


Fig. 3. Molecular structures of pyrimidine with anticancer potential.

Safinaz et al. 2019 synthesized novel fused pyrimidine analogs and tested for anticancer activity. Among all compounds (**16**) and (**17**) exhibited significant anticancer activity against cancer cell lines ($IC_{50} = 0.01$ µM, PC-3, $IC_{50} = 0.01$ µM, MCF-7) compared with the standard (doxorubicin, $IC_{50} = 0.04$ µM). The observed activity is due to the presence of chloro, 4-methylbezylidene, and pyrimidine moiety (Fig-4) [**3**].

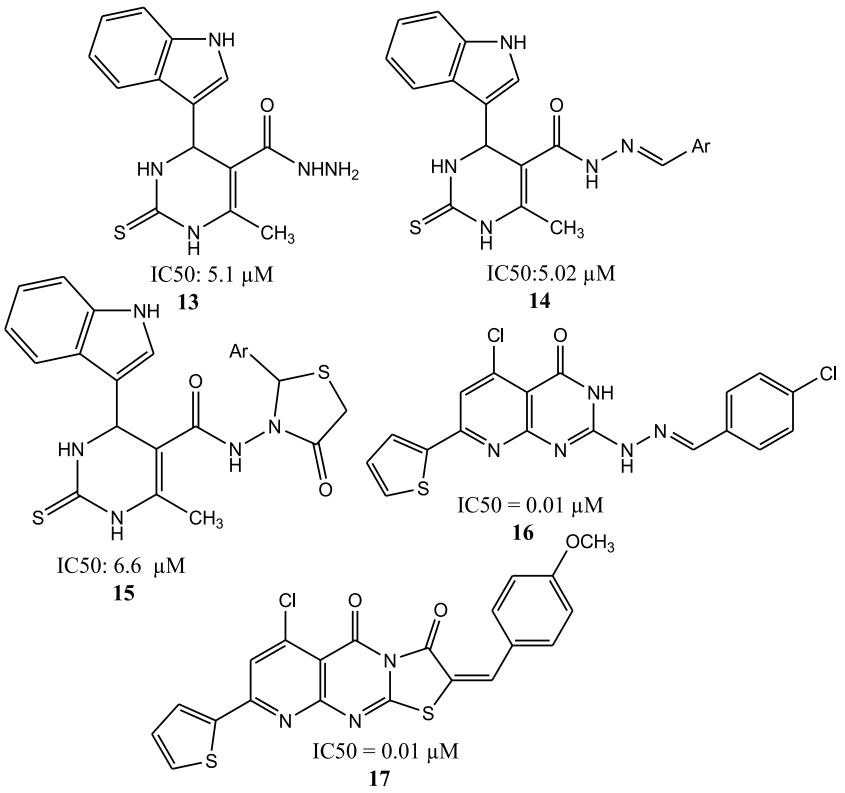


Fig. 4. Molecular structures of pyrimidine with anticancer potential.

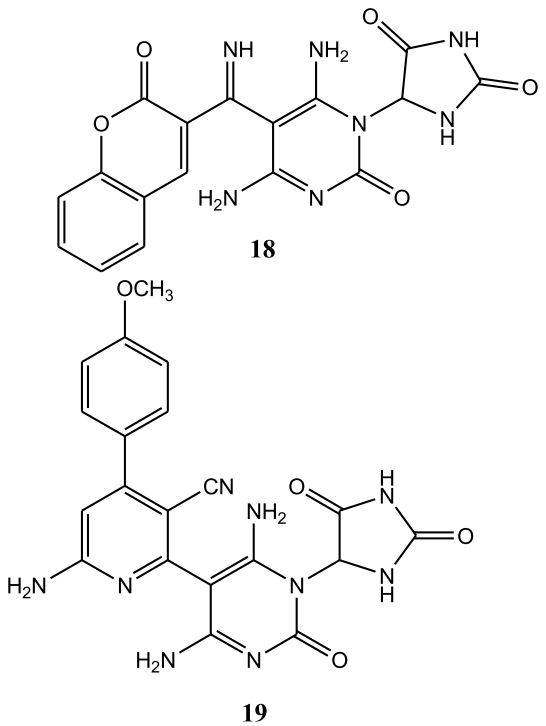


Fig. 5. Molecular structures of pyrimidine with analgesic potential.

2.3. As an anti-inflammatory & analgesic agent

Anti-inflammatory drugs (NSAIDs) have a wide therapeutic benefit that ranges from the treatment of fever, inflammation, and mild pain. Most commonly prescribed drugs like diclofenac, ibuprofen and mefenmic acid, etc [23].

Karam Ahmed et al. 2018. developed novel pyrimidine analogs & screened for anti-inflammatory & analgesic activity. Among them compounds **18** (Analgesic activity (%): 2.38 ± 0.08, 3.18 ± 0.08, 2.43 ± 0.03, 125.1 ± 1.68 and 97.56 ± 0.55 & Anti-inflammatory activity (%): 0.82 ± 0.02, 0.84 ± 0.01, 29.34 ± 2.97, 32.08 ± 2.05) and **19** (Analgesic activity (%): 2.20 ± 0.11, 3.15 ± 0.07, 2.40 ± 0.06, 119.5 ± 1.45 and 96.5 ± 0.25) showed good analgesic & anti-inflammatory potential. The enhanced activity may be due to the presence of coumarin and 4-methoxyphenylpyridine moiety (Fig. 5) [24].

Siham Lahsani et al. 2018. developed novel pyrimidine derivatives & evaluated for anti-inflammatory activity. Among all compound (**20**) exhibited satisfactory anti-inflammatory activity (RBC = 0.179 ± 0.01775 & RBC (% hemolysis) = 101.6216 ± 0.0005) compared with standard (RBC = 0.132 ± 0.002251 & RBC (% hemolysis) = 102.851 ± 0.00076). The observed activity is may be due to the presence of thiazolo-pyrimidine scaffold [25].

Naglaa Mohamed Ahmed et al. 2020. Prepared new pyrimidine analogs and tested them for anti-inflammatory potential. Among all compounds (**21**), (**22**) & (**23**) exhibited 61–86% anti-inflammatory potency compared with standard (Ibuprofen, 69%) at 1 h interval post-carrageenan range from 22 to 74%. The enhanced activity may be due to the presence of thieno-pyrimidine moiety [26].

Mohamed H M AbdEl-Azim et al. 2020 synthesized novel pyrano [2,3-d]pyrimidine analogs & tested for anti-inflammatory potency. Among them compound (**24**) exhibited remarkable in vitro anti-inflammatory activity (Cox-1 IC_{50} (μm) = 13.13 ± 0.15 m, Cox-2 IC_{50} (μm) 0.04 ± 0.02) & TNF-α IC_{50} (nm) 3.50 ± 0.10) compared with standard drugs (celecoxib, quercetin, and certolizumab, 0.04 ± 0.01, 3.34 ± 0.12, and 6.90 ± 0.26). The enhanced activity may be due to the presence of chloro group & thino-pyrimidine moiety (Fig. 6) [27].

2.4. As anti-oxidant agent

Antioxidant scavenging of free radicals is an important biological function and it prevents oxidative damage in the body. Radical–induced oxidative damage in the body is associated with several diseases. Antioxidants from both natural and synthetic sources can scavenge free radicals and prevent oxidative damage [28].

Esvet Akbas et al. 2019. Prepared novel pyrimidine analogs & evaluated them for antioxidant activity. Among all compounds (**25**) exhibited satisfactory anti-oxidant potency (IC_{50}: 155.80 μm) compared with standard (Tocopherol, IC_{50}:145.59 μm). The observed

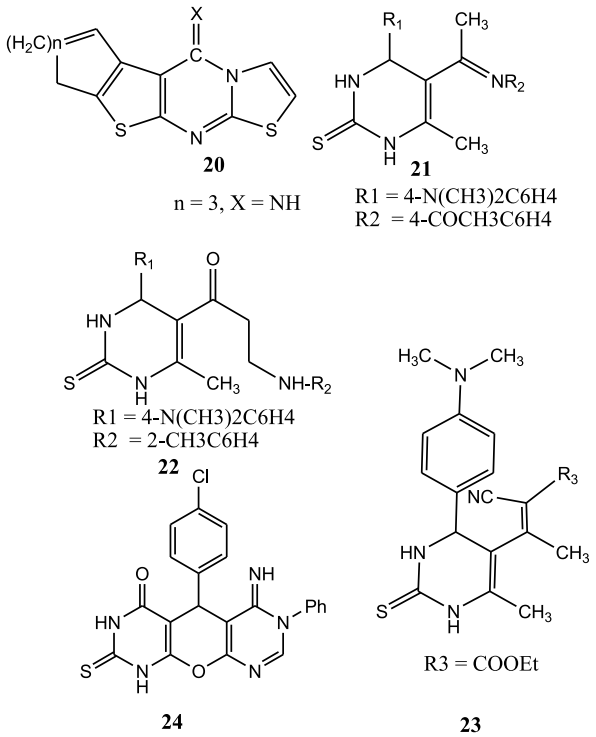


Fig. 6. Molecular structures of pyrimidine with analgesic and anti-inflammatory potential. Naglaa Mohamed Ahmed et al., 2020. Prepared new pyrimidine analogs and tested them for antiinflammatory potential. Among all compounds (**21**), (**22**) & (**23**) exhibited 61–86% antiinflammatory potency compared with standard (Ibuprofen, 69%) at 1 h interval postcarrageenan range from 22 to 74%. The enhanced activity may be due to the presence of thienopyrimidine moiety [**27**].

activity may be due to the presence of pyrimidine scaffold [29].

Ahmed A Hadi et al. 2020. developed novel pyrazolo-pyrimidine analogs & evaluated for antioxidant activity. Among all compounds (**26**) exhibited good antioxidant activity (Inhibition: 82%) compared with the standard (Inhibition: 94%). The observed activity is due to the presence of hydroxy naphthalene and pyrazolo-pyrimidine scaffold [30].

Hatem A Abuelizz et al. 2019 synthesized novel pyrido-triazolopyrimidine analogs & tested for antioxidant potential. Among all compounds (**27**) & (**28**) exhibited good potency of antioxidants (FRAP: 973 & 1143 μmol, Trolox/100 g) compared with the standard. The enhanced activity may be due to the presence of -S-R (Electron-rich sulfur group) and pyrimidine scaffold (Fig. 7) [31].

Jyoti Rani et al. 2017. developed novel tetrahydroimidazo-pyrimidine analogs & evaluated for antioxidant potential. Among all compounds (**29**) & (**30**) exhibited satisfactory antioxidant potential (IC_{50} values = 46.31 & 48.81 μg/mL) compared with standard (Ascorbic acid IC_{50}: 42.52 μg/mL). The observed activity is due to the presence of active groups (methoxy OCH_3 & OH groups) on benzylidene moiety [32].

Bhadraiah U K et al. 2021. developed novel bicyclic pyrimidine analogs and evaluated for antioxidant activity. Among which, compound (**31**) exhibited a strong scavenging effect on the stable nitric oxide radical (IC_{50}: 2.50 ± 0.65 μg/mL) compared with standard (Ascorbic acid: IC_{50}: 5.35 ± 0.68 μg/mL). The enhanced activity may be due to the presence of chloro & methoxy group at the pyrimidine scaffold (para position) [33].

Abrar A. Bayazeed et al. 2020 synthesized novel pyrimidine analogs and tested for antioxidant activity. Among which, compound (**32**) & (**33**) exhibited good antioxidant activity (Percent inhibiton: 86.07% & 85.29%) compared with standard (Ascorbic acid: 88.23%). The observed activity may be due to the presence of acetyl & benzoyl substituent group at the pyran moiety (Fig. 8) [34].

2.5. As cardiac agent

Due to hypertension, the death rate is increased worldwide and one billion people suffer from hypertension universally and causing deaths nearer to nine million every year. Cardiovascular-related diseases prevention and treatment is a big challenge.

Nadeem Irshad et al. 2021 observed the anti-hypertensive potency in some selected pyrimidine analogs. Among all compounds **34** (45 ± 0.5, 56 ± 0.5, 64 ± 0.4 mmHg and 378 ± 0.5 bpm), **35** (89 ± 0.5, 81 ± 0.6, 82 ± 0.5 mmHg, 373 ± 0.5 bpm), **36** (50 ± 0.6, 61 ± 0.6, 60 ± 0.3 mmHg, 381 ± 0.5 bpm) and **37** (51 ± 0.4, 43 ± 0.5, 67 ± 0.5 mmHg, 378 ± 0.4 bpm) exhibited BP-lowering potential compared with standard (Nifedipine: 43 ± 0.5, 39 ± 0.4, 59 ± 0.4 mmHg and 381 ± 0.6 bpm). The enhanced activity may be due to the presence of substituted-pyrimidine scaffold (-Cl & –OH) (Fig. 9) [35].

2.6. As an anti-diabetic agent

Diabetes mellitus is a severe problem around the world, 463 million people suffer from this and it may rise to 578 million (Approx estimation) by 2030 [36].

Bassyouni F et al. 2021 synthesized fused pyrimidine analogs & tested for anti-diabetic activity. Among all compounds (**38**) & (**39**)

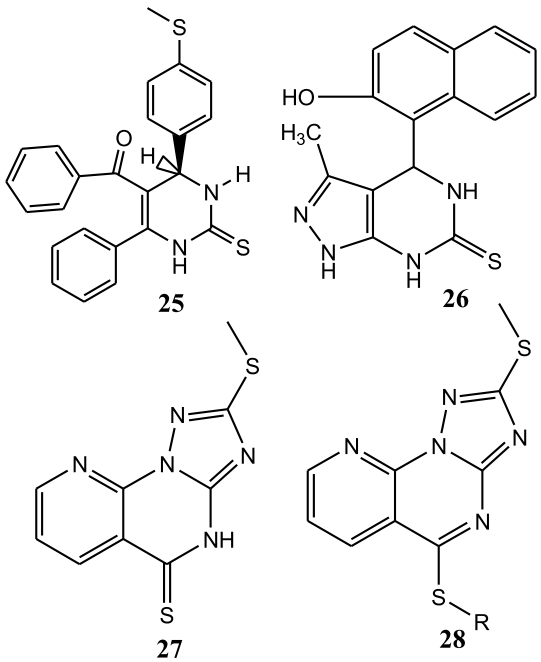


Fig. 7. Molecular structures of pyrimidine with antioxidant potential.

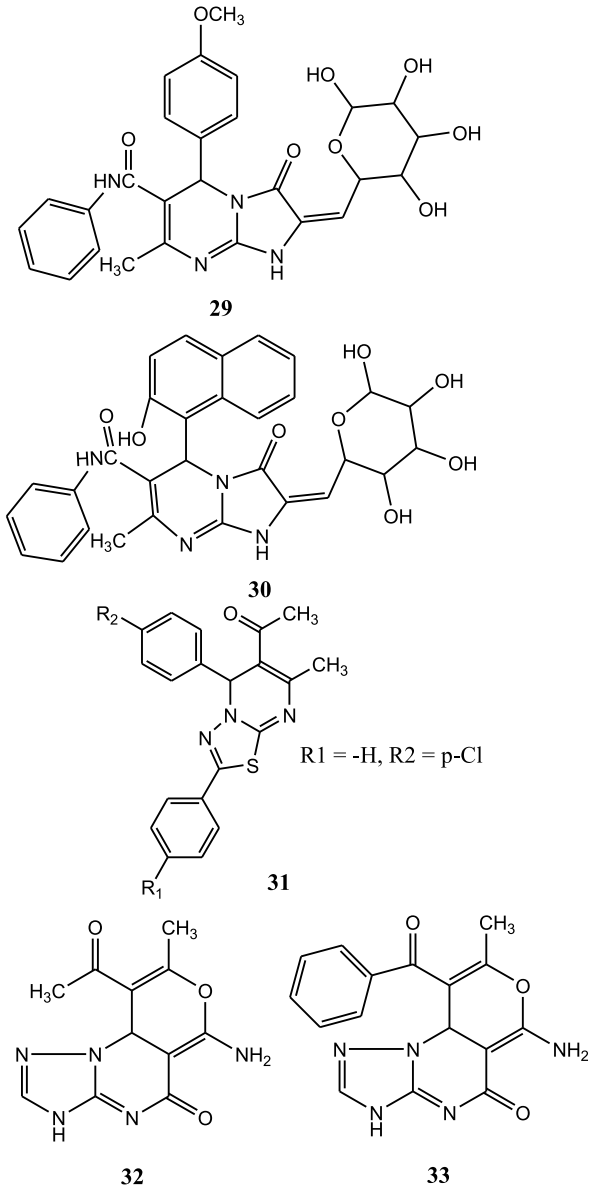


Fig. 8. Molecular structures of pyrimidine with antioxidant potential.

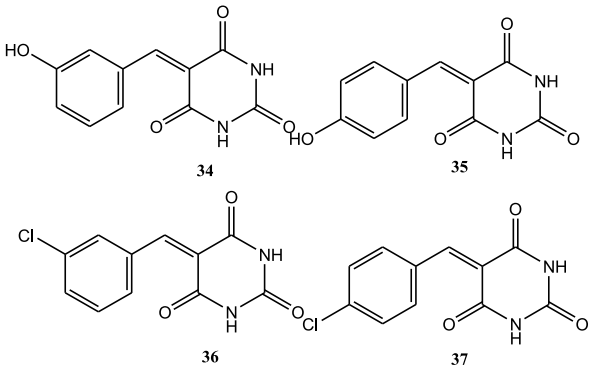


Fig. 9. Molecular structures of pyrimidine as cardiac agents.

(Glucose Level: 122.4 ± 3.2, mg/dL & 116.5 ± 7.2, α-amylase level: 117.6 ± 1.51 & 78.41 ± 1.04 U/L) showed good anti-diabetic potential compared to those of positive control (Glucose Level: 408.3 ± 36.32 mg/dL & α-amylase level: 317.4 ± 12.86 U/L). The observed activity may be due to the presence of pyridine & thino-pyrimidine scaffold (Fig. 10) [10].

2.7. As an anti- HIV agent

HAART-Highly Active Antiretroviral Therapy showed positive benefits in treating AIDS patients with HIV-1 infection. The use of different screening tests for the severe infection with human immunodeficiency virus (HIV) and based on the experimental test results we can understand the immune system response to HIV infection. HIV can be cured with medications, which slow down or stop the virus replication. Further, the body's immunity starts repairing it and also stops further severe damage. A different combination of HIV drugs is used for the treatment because HIV may get quickly resistant [37,38].

Kang D et al. 2019 synthesized novel pyrimidine (dihydrofuro) analogs & screened for anti-HIV activity. Among all compounds (**40**) showed satisfactory potential against HIV-1 strains (EC_{50}: 0.9–8.4) compared to standard (Etravirine, EC_{50}: 5.1 nM). The enhanced activity may be due to the presence of pyridine & substituted pyrimidine scaffold [39].

Huang B et al. 2021 prepared novel piperidinyl-substituted pyrimidine analogs & tested for their anti-HIV potential. Among which compound (**41**) was the most active one (EC_{50} = 4.29 M, CC50 > 247 μM) against HIV-1 WT strain compared with standard drug. The observed activity is may due to the presence of phenyl ring with electron-donating groups at 4-position and also the presence of pyrimidine scaffold [**38**].

Goudgaon et al. 1991 synthesized novel pyrimidine analogs & tested for their anti-HIV potential. Among the compounds (**42**) exhibited good antiviral potency against primary human lymphocytes (HIV-1, 17.5 & HIV-2, >100). The enhanced activity may be due to the presence of a substituted-thino-pyrimidine scaffold [40].

B Chuan et al. 1994 synthesized novel pyrimidine analogs & evaluated for anti-HIV-1 activity. Among which compound (**43**) exhibited good anti-HIV activity (IC_{50} = 24 + 0.1 μM) against MT-2 cell lines. The observed activity may be due to the presence of thio-pyridine derivative & substituted-pyrimidine scaffold (Fig. 11) [41].

2.8. As an anthelmintic agent

Anthelmintics have belonged to a group of antiparasitic drugs and these give severe problems to infected people. Anti-parasitic drugs will kill the parasitic worms without causing any damage to the host.

David I Ugwu et al. 2018 synthesized new pyrimidine analogs bearing carboxamide and sulphonamide moieties and tested for anthelmintic activity. Among all compounds (**44**) exhibited satisfactory anthelmintic activity (Paralyzing time: 37, 26 & 19, min) compared to that of Albendazole (Paralyzing time: 28, 20 & 10, min). The enhanced activity may be due to the presence of nitrophenyl and pyrimidine scaffold [**8**].

Sudha Rani K et al. 2018 prepared 4,6- disubstituted pyrimidine-2- one derivatives & screened for antihelmintic potential. Among which the compound (**45**) showed high potential (Paralysis time: 7 ± 0.763 min, Death time: 11 ± 0.611 min) compared to the standard drug (Albendazole: Paralysis time: 2.51 ± 1.1 min, Death time: 18 ± 2.1 min) (Fig-12). The observed activity may be due to the presence of a phenyl-pyrimidine scaffold (Fig. 12) [42].

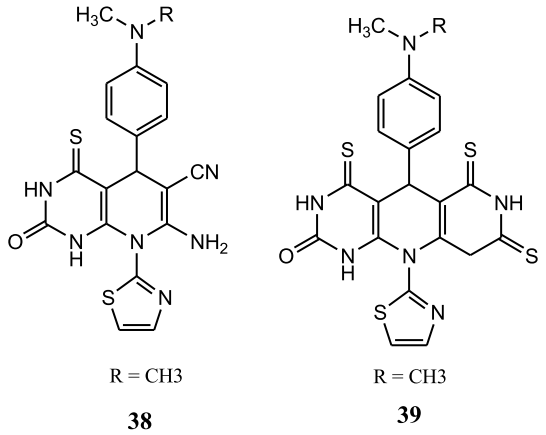
2.9. As central nervous system depressant

Barbiturates are a class of drugs derived from pyrimidinetriones and are commonly called barbituric acids which slow down the brain activity and relax the muscles and especially these may be used before surgery. The phenobarbital, meberal, seconal, nembutal, amytal, and pentothal are closely similar to barbiturates. Based on the above applications our group has been synthesized and found to be clinically useful as sedative and hypnotic drugs. N M Goudgaon et al. 2011 synthesized novel 5-substituted pyrimidin-triones & tested for CNS depressant activity. Among all compounds **46** (Motor Activity Score: 63.16 + 10.91, 23.33 + 4.73 & 21.33 + 5.11 min) & **47** (Motor Activity Score: 60.66 + 11.36, 46.00 + 10.44, 42.16 + 10.40 min) showed significant CNS depressant potential compared with standard drug (Diazepam, 80.00 + 7.7 43.66 + 13.41 37.33 + 10.88 min). The enhanced activity may be due to the presence of pyrazole-aldehyde and substituted-pyrimidine scaffold (Fig. 13) [43].

Jeelan Basha N et al. 2021 recently reviewed that piperazine bearing pyrimidine and fused pyrimidines such as buspirone (**48**), ritanserin (**49**), and risperidone (**50**) act as anxiolytic agents (Fig. 14) [44].

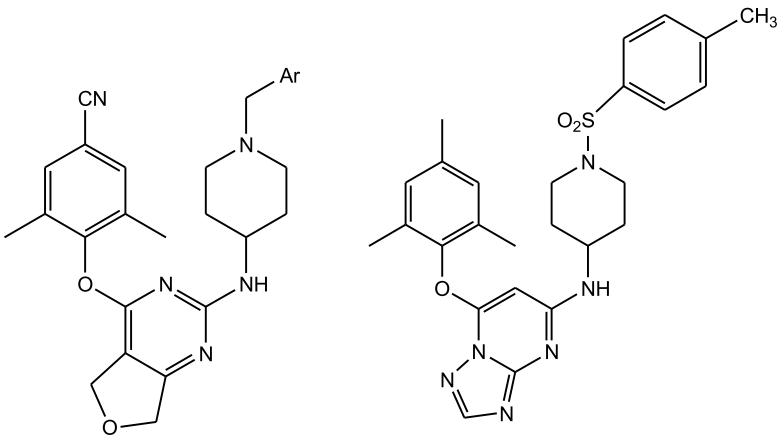
3. Commercially available pyrimidine drugs

Dosatinib (**51**) is used to treat chronic myelogenous leukemia and acute lymphoblastic leukemia. Dasatinib is a pan-Src kinase inhibitor [25,45]. Etravirine (**52**) and Rilpivirine (**53**) are popularly meant for HIV-1 (NNRTI) (Fig. 15) [39]. The synthesis and biological potency of other versatile scaffolds such as Coumarin [46–50]. Benzimidazole [51,52] and Pyrazole derivatives acting as antimicrobial agents [53,54]. Some recent review articles on novel pyrimidine analogs with various pharmacological activities may help the young researcher for designing and developing new active drugs [55–59].

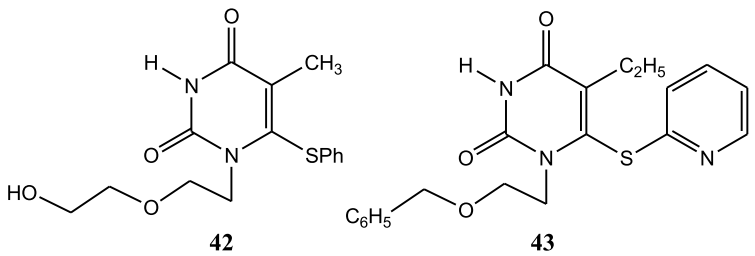


38 39

Fig. 10. Molecular structures of pyrimidine as antidiabetic agents.



40 41



42 43

Fig. 11. Molecular structures of pyrimidine with anti-HIV potential.

4. Conclusion

Pyrimidine and its analogs majorly contributed to the field of medicinal chemistry. The recent literature survey reveals that almost all drugs are associated with pyrimidine scaffold. In this review manuscript, the recent development and biological approaches are highlighted. The chloro, amine, fluorine, bromine, amino-pyrimidine, 4-methoxyphenylpyridine, hydroxy naphthalene, coumarin ring, pyrazolo-pyrimidine, thino-pyrimidine, phenyl-pyrimidine scaffold presence in various positions of the aromatic ring may enhanced biological potential. Further, the medicinal potency and the structure-activity relationship of pyrimidines such as antimicrobial, anticancer, anti-inflammatory, analgesic, anti-diabetic, anti-HIV, anthelmintic, CNS depressants, and cardiac agents have been discussed. Finally, this review article may attract the researchers to design and develop a new synthetic route with more active and least toxic.

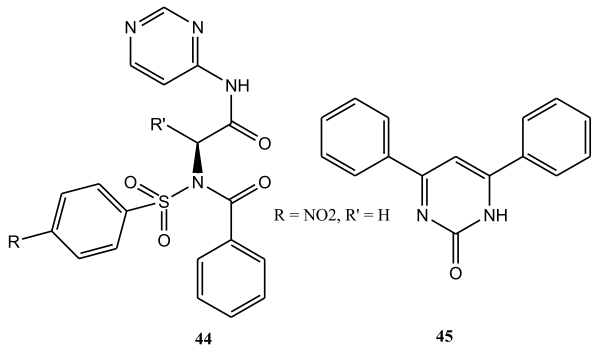


Fig. 12. Structures of pyrimidine with anthelmintic potential.

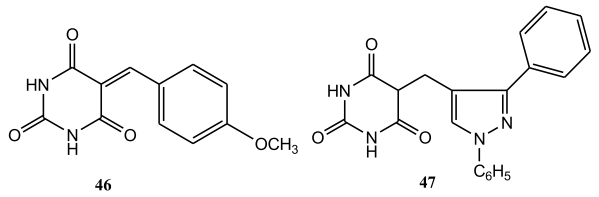


Fig. 13. Molecular structures of pyrimidine with CNS depressant potential.

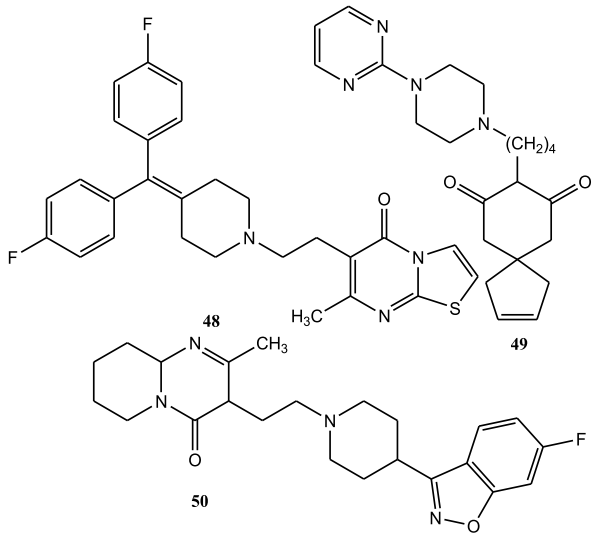


Fig. 14. Molecular structures of pyrimidine with anxiolytic potential.

Declarations

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

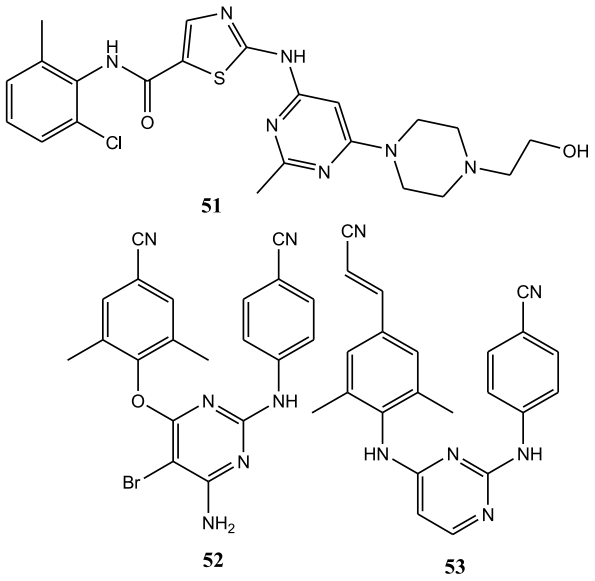


Fig. 15. Commercially available pyrimidine scaffold associated drugs.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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