Asian Journal of Chemistry; Vol. 37, No. 12 (2025), 2897-2930
ASIAN JOURNAL OF CHEMISTRY
https://doi.org/10.14233/ajchem.2025.34772

*REVIEW*

# Pyrimidine Scaffolds as Versatile Platforms for Therapeutic Potential: A Review

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*Received*: 28 August 2025 *Accepted*: 20 October 2025 *Published online*: 30 November 2025 AJC-22181

Nitrogen-bearing heterocycles continue to shape modern medicinal chemistry owing to their structural adaptability and capacity to participate in diverse biochemical interactions. Within this class, pyrimidine frameworks have emerged as especially influential, providing a chemically economical core from which varied pharmacological profiles can be engineered. Their modular architecture supports precise functionalization, enabling the design of molecules with activities spanning antiviral, anticancer, anti-inflammatory, antibacterial, antitubercular, antimalarial and neuroactive domains. Recent studies demonstrate that integrating pyrimidine cores with complementary heterocycles particularly thiazole units can substantially enhance target engagement, strengthen metabolic stability and yield more favourable pharmacodynamic profiles. This review summarizes the current progress in the development of pyrimidine-based scaffolds, emphasizing the relationship between structural modification and biological response. The collective findings underscore the continued relevance of pyrimidine chemistry as a driver in the discovery of next-generation therapeutic agents.

**Keywords: Fused-pyrimidine derivatives, Pharmacophore, FDA approved drugs, Drug discovery.**

## INTRODUCTION

Nitrogen-containing pharmacophores possess an indispensable and pivotal role in the medicinal chemistry and drug development process [1]. Several four membered nucleus (β-lactam ring and azetidines), five membered nucleus (pyrolidine, benzimidazole, imidazole, oxadiazole, thiazole, oxazole, isoxazole, pyrazoles and 1,2,3-triazole) and six-membered (quinoline, isoquinoline, pyrimidine, quinazoline, piperidine, pyridine) nitrogen containing pharmacophores are present in various therapeutically active natural products such as solasodine, piperidine, batzelline, phidianidine A, phidianidine B, quisqualic acid, quinine, caffeine, tunicamycin, cupramycin, morphine, berberin, codeine, emetin, lutonin A, bouchardatine, 2,6-lutidine, dragmacidins D and echinobetaine B [2-10]. Incorporation of nitrogen to aromatic and heterocyclic ring systems adds some unique and admirable properties like accepting and donating a proton and a power to establish other types of weak intramolecular bonding interactions like dipole-dipole interactions, hydrogen bonding, π-stacking, hydrophobic interactions and van der Waals forces of attractions with various therapeutically important molecular targets *i.e.* enzymes and receptors. Due to these exciting properties and electron-rich nitrogen in nitrogen containing pharmacophores deliver high solubility and excellent affinity for biological targets responsible to elicit broad spectrum bioactivities [11-14].

Pyrimidine is a six membered aromatic ring containing molecule with two nitrogen at 1 and 3 positions and belongs to the class of diazines (dia = two + azine = nitrogen). The ionization constant ($pK_a$) of pyrimidine at mono-protonated state is 1.3, whereas $pK_a$ value of -6.9 [15,16]. It is quite less basic than pyridine. It is a polar molecule with dipole moment ranges from 2.1 to 2.4 debye [17]. Due to the presence of electronegetive nitrogen atom at 1 and 3 position the π-elcetron density at 2, 4 and 6 carbon atom of the ring is less and are π-electron deficient. Due to inductive elcetronegetive effect position 5 of pyrimidine ring is also electron deficient but less than 2, 4 and 6 positions [18]. Pyrimidine scaffold (Fig. 1) is a highly

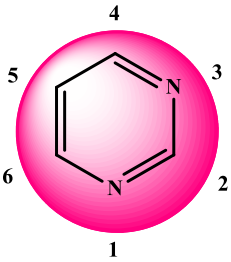
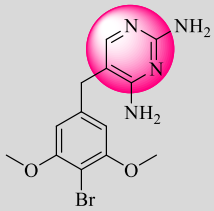
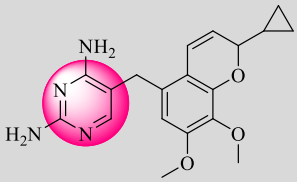
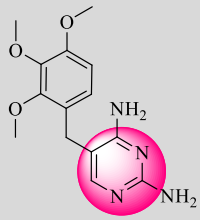
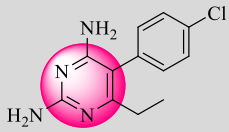
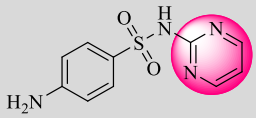
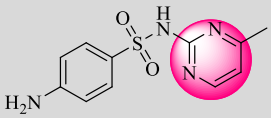
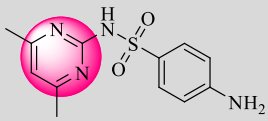
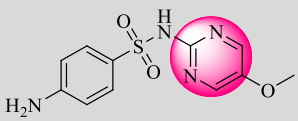



Fig. 1. Structure of pyrimidine

privileged pharmacophore in medicinal chemistry as it exhibited excellent pharmacological activities like antimicrobial, analgesic, antiviral, anticancer, anti-inflammatory, antioxidant, analgesic, antidiabetic, antirheumatic, antihypertensive, anti-leishmanial, anti-alzheimer and antimalarial [19-29]. Indispensible importance and role of pyrimidine nucleus in medical science could be understand from the fact that it served as a basic pharmacophore in most of the clinically used drugs. The clinically used pyrimidine-based drugs with their structure and uses are presented in Table-1.

TABLE-1
PYRIMIDINE BASED CLINICALLY USED DRUGS

| Name of drug | Structure | Use | Ref. |
|---|---|---|---|
| Brodiprim |  | Antibacterial | [30] |
| Iclaprim |  | Antibacterial | [31] |
| Trimethoprim |  | Antibacterial | [32] |
| Pyrimethamine |  | Antimalarial | [33] |
| Sulfadiazine |  | Antibacterial | [34] |
| Sulfamerazine |  | Antibacterial | [35] |
| Sulfadimidine (sulfamethazine) |  | Antibacterial | [36] |
| Sulfamethoxydiazine |  | Antibacterial | [37] |

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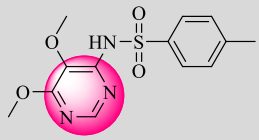
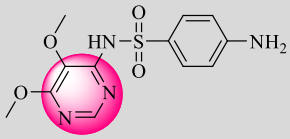
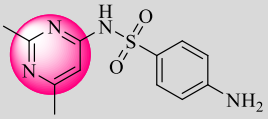
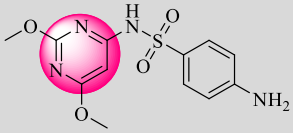
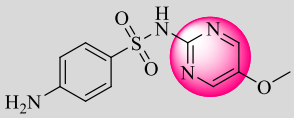
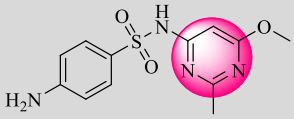
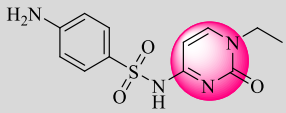
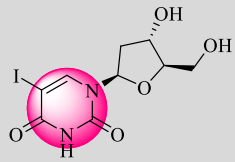
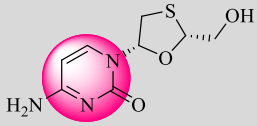
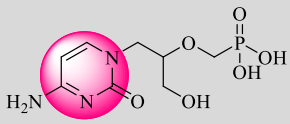
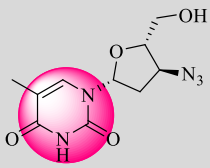
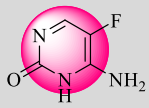
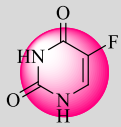
|---|---|---|---|
| Sulfamethyldiazine |  | Antibacterial | [38] |
| Sulfadoxine |  | Antibacterial | [39] |
| Sulfisomidine |  | Antibacterial | [40] |
| Sulfadimethoxine |  | Antibacterial | [41] |
| Sulfamethoxine |  | Antibacterial | [42] |
| Sulfamethomidine |  | Antibacterial | [43] |
| Sulfacytine |  | Antibacterial | [44] |
| 5-Iododeoxyuridine |  | Antiviral | [45] |
| Lamivudine |  | Anti-HIV | [46] |
| Cidofovir |  | Antiviral | [47] |
| Zidovudine |  | Anti-HIV | [48] |
| Flucytosine |  | Antifungal | [49] |
| 5-Fluorouracil |  | Anticancer | [50] |

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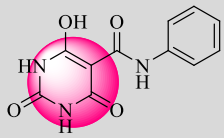
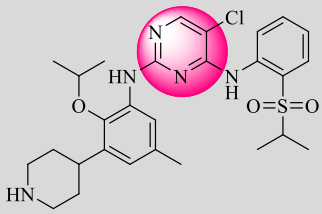
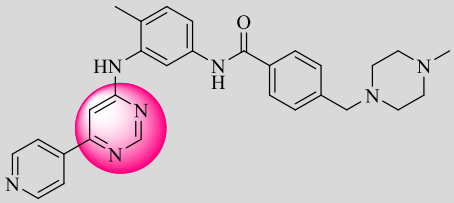
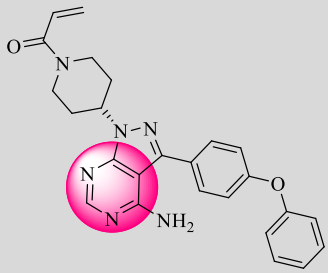
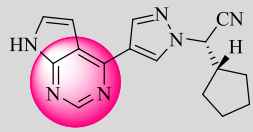
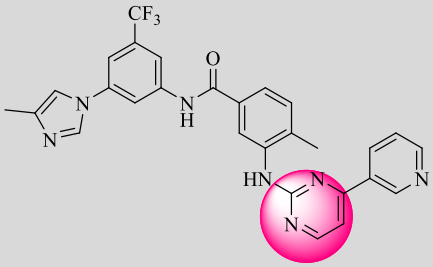
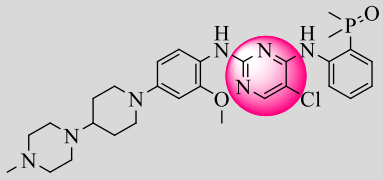
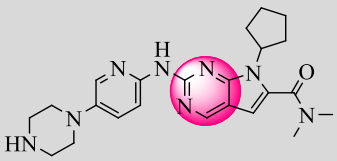
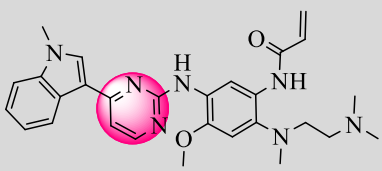
|---|---|---|---|
| Merbarone |  | Anticancer | [51] |
| Ceritinib (LDK378) |  | Anticancer | [52] |
| Imatinib |  | Anticancer | [53] |
| Ibrutinib (IBR) |  | Anticancer | [54] |
| Ruxolitinib (INC424) |  | Anticancer | [55] |
| Nilotinib |  | Anticancer | [56] |
| Bringatinib |  | Advanced ALK-positive metastatic non-small cell lung cancer | [57] |
| Ribociclib |  | Breast cancer | [58] |
| Osimertinib |  | Advanced ALK-positive metastatic non-small cell lung cancer | [59] |

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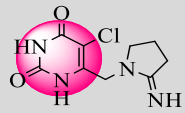
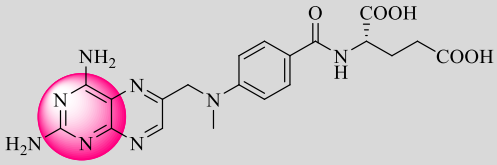
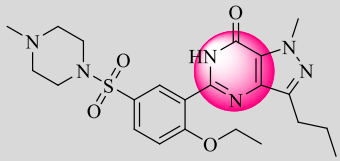
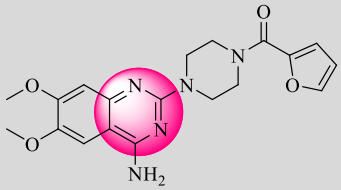
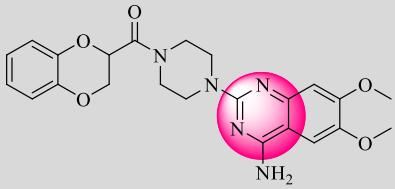
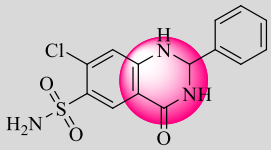
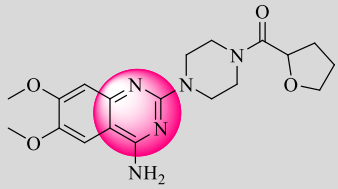
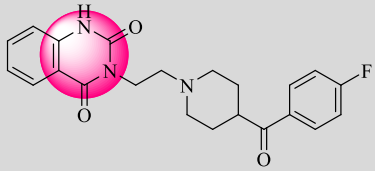
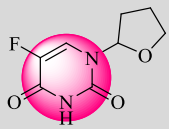
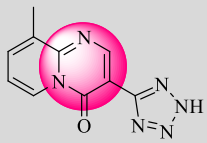
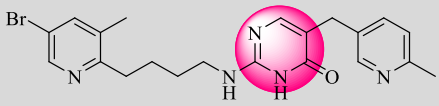
|---|---|---|---|
| Tipiracil |  | Metastatic colorectal cancer | [60] |
| Methotrexate |  | Antimalarial, anticancer, anti-inflammatory | [61-63] |
| Sildenafil |  | Phosphodiesterase-5 (PDE5) inhibitor, treatment of erectile dysfunction | [64,65] |
| Prazocin |  | Antihypertensive | [66] |
| Doxazosin |  | Antihypertensive | [67] |
| Fenquizone |  | Diuretic | [68] |
| Terazocin |  | Antihypertensive | [69] |
| Ketanserin |  | Antihypertensive | [70] |
| Tegafur |  | Anticancer | [71] |
| Pemirolast |  | Antihistaminic | [72] |
| Temelastine |  | Antihistaminic | [73] |

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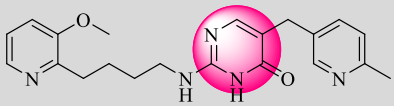
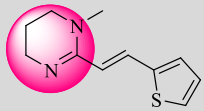
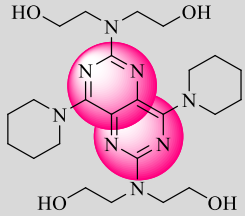
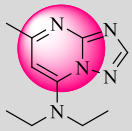
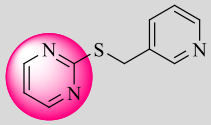
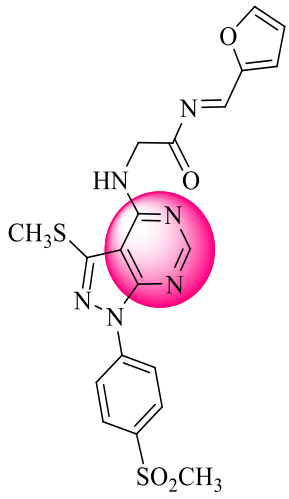
|---|---|---|---|
| Icotidine |  | Antihistaminic | [74] |
| Pyrantel |  | Anthelmintic | [75] |
| Dipyridamole |  | Vasodilators | [76] |
| Trapidil |  | Vasodilators | [77] |
| Tasuldine |  | Expectorant and mucolytic | [78] |

Various scientists and researchers are still working on designing and developing more potent, selective and safer pyrimidine-based molecules for treating different diseases. A comprehensive search of the literature was conducted using google scholar, scopus, web of science database index to identify studies reporting the design, synthesis or biological evaluation of pyrimidine-based derivatives. From all databases and supplementary sources, more than 300 records were initially retrieved. After removing repeated entries, the remaining studies underwent title and abstract screening based on predefined inclusion criteria focused on relevance to pyrimidine chemistry and associated pharmacological properties. Articles clearly unrelated to the chemical class, lacking biological data, or presenting inadequate methodological information were eliminated at this stage.

Full-text assessment was then carried out for the set of potentially eligible studies. Articles were also excluded for reasons such as incomplete experimental details, absence of validated assays, insufficient compound characterization or failure to meet quality benchmarks for biological evaluation. Following the rigorous filtering process, only the studies that satisfied all methodological and thematic requirements were included in the final qualitative synthesis. The selection steps, decisions, and outcomes were documented according to the PRISMA framework to ensure transparency and reproducebility. A brief review of notable current advancements in the development of novel and effective pyrimidine-based molecules is discussed in the following sections.

**Anti-inflammatory agents:** Abdelall *et al.* [79] had reported triazole, pyrazole, oxadiazole and Schiff base linked pyrazolopyrimidine derivatives as potent anti-inflammatory agents. Two most active compounds **1** and **2** had inhibited COX-2 enzyme with $IC_{50}$ value of 0.10 μM and 0.16 mM, respectively. Both of these compounds had shown superior anti-inflammatory potency than celecoxib during *in vitro* COX-2 enzyme inhibition and *in vivo* carrageenan induced rat paw edema assay. Tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine derivatives were synthesized and evaluated as anti-inflammatory agents by Zhang *et al.* [80] using LPS induced *in vitro* cell assay and *in vivo* carrageenan induced rat paw edema assay. Cellular level of cytokines, TNF-α and IL-6 level were significantly reduced up to 70% and 90% at 10 μM concentration by compound **3** and **4** respectively as compared to LPS control. Somakala *et al.* [81] had reported pyrazolo[3,4-*d*]-pyrimidine benzamide derivatives as potent p38α MAPK enzyme inhibitor for the treatment of inflammation. Among the synthesized derivatives, two compounds **5** and **6** had shown strong *in vitro* bovine serum albumin denaturation inhibition potential comparable to that of diclofenac sodium. The half-maximum inhibition potential ($IC_{50}$) of 0.032 ± 1.63 μM and 0.038 ± 0.83 μM was shown by compounds **5** and **6** against p38a MAP kinase, respectively. Carrageenan induced rat paw edema inhibition of 83.73% and 76.35 % was shown by compounds **5** and **6**, respectively. Two pyrazolo[3,4-*d*]pyrimidine derivatives with moderate COX-2 selectivity were synthesized by Atatreh *et al.* [82]. These compounds (**7** and **8**) were also evaluated using *in vivo* carrageenan induced rat paw edema method for their anti-inflammatory potentials. A potent pyrazolo[4,3-*d*]pyrimidine derivative **9** was designed and synthesized by Wang *et al.* [83] had shown good IL-6, TNF-α and NO inhibition potential ($IC_{50}$) of 2.64 μM, 4.38 μM and 5.63 μM, respectively during *in vitro* LPS induced inflammation assay in RAW264.7 macrophages.

Pyrazole linked pyrazolo[4,3-*d*]pyrimidine derivatives were reported by Tageldin *et al.* [84]. Two most active compound **10** and **11** from this series inhibited COX-2 enzyme with $IC_{50}$ value of 0.87 μM and 0.54 μM, respectively. Compound **11** had exhibited superior COX-2 inhibition potency greater than



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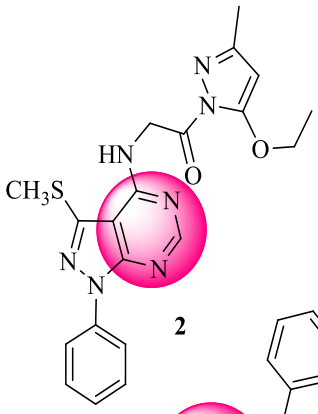

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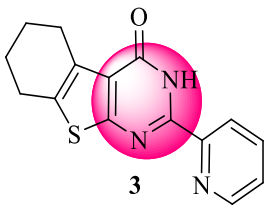

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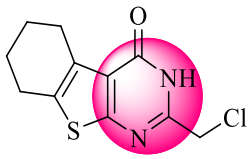

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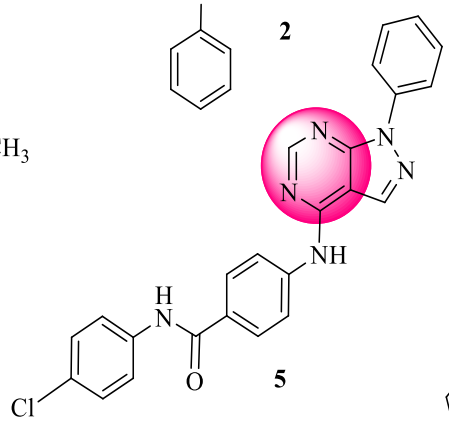

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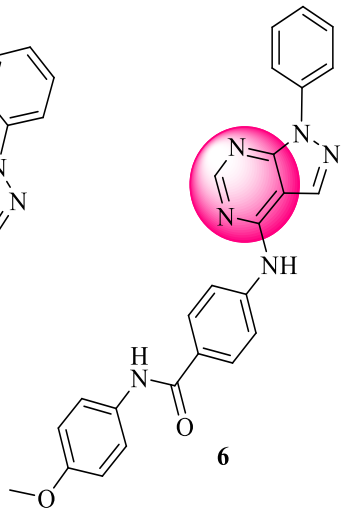

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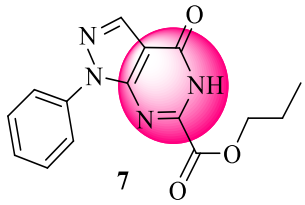

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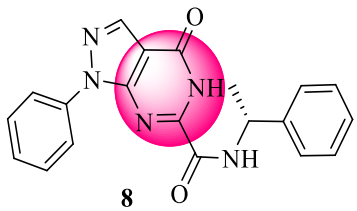

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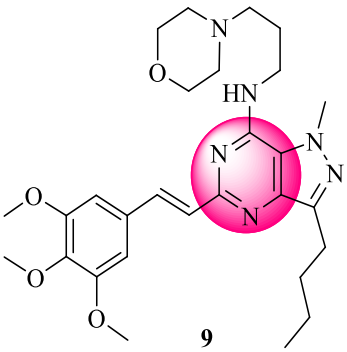

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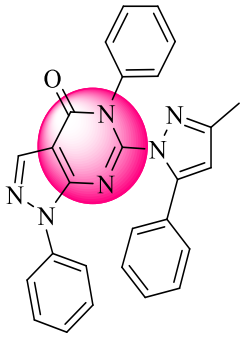

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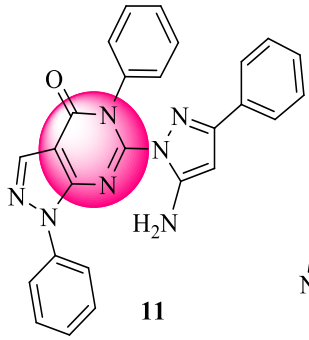

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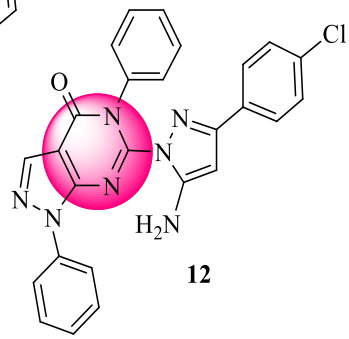

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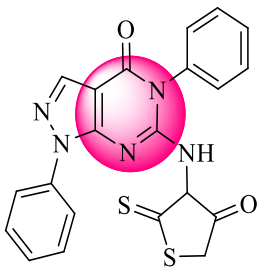

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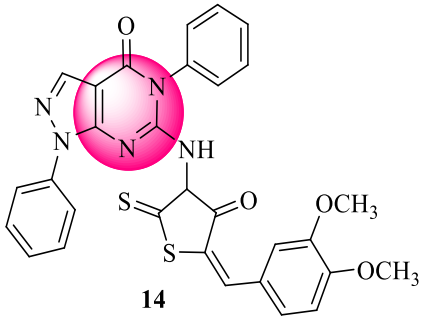

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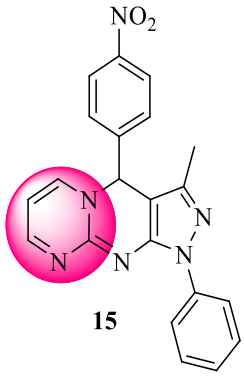

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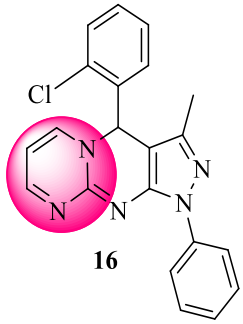

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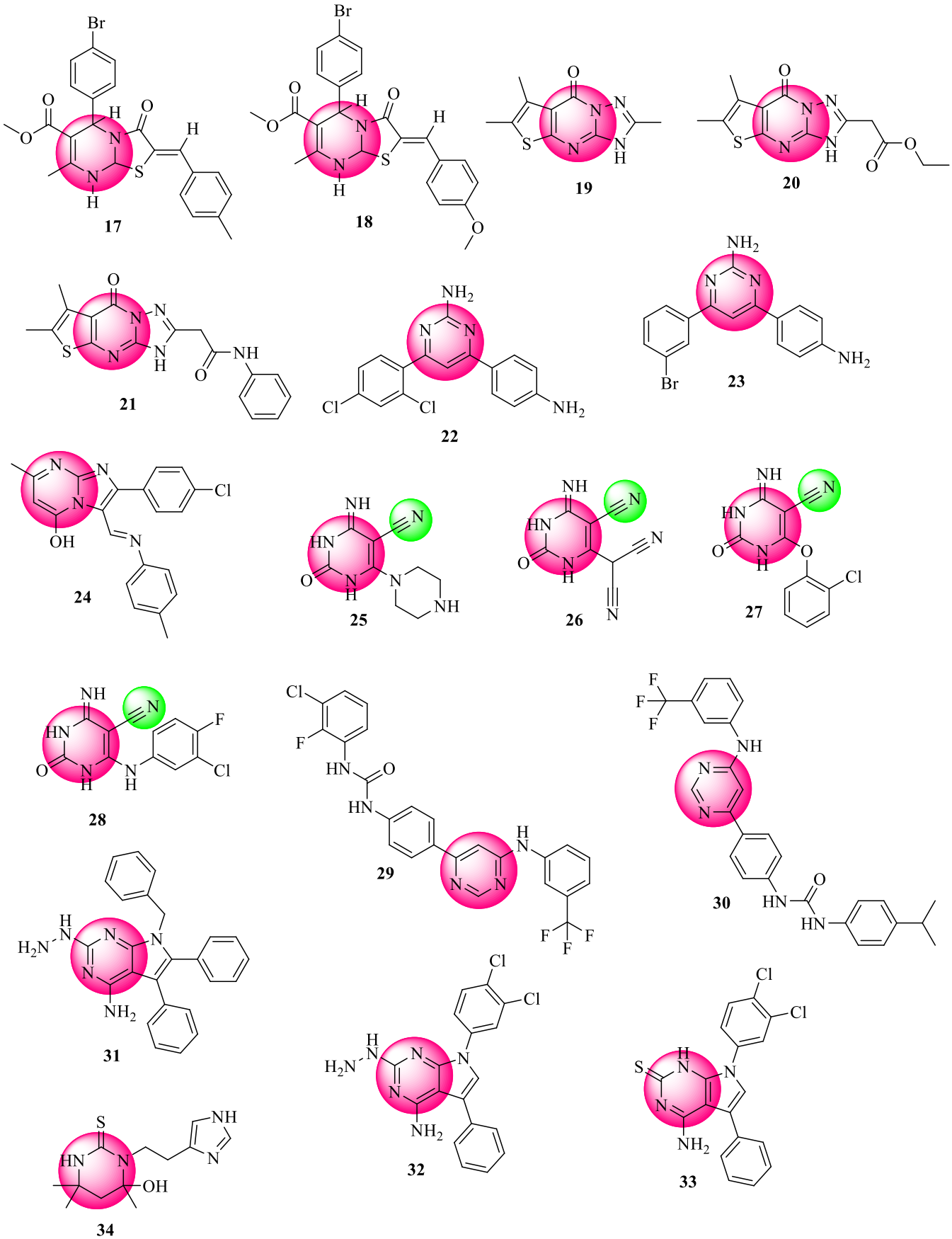
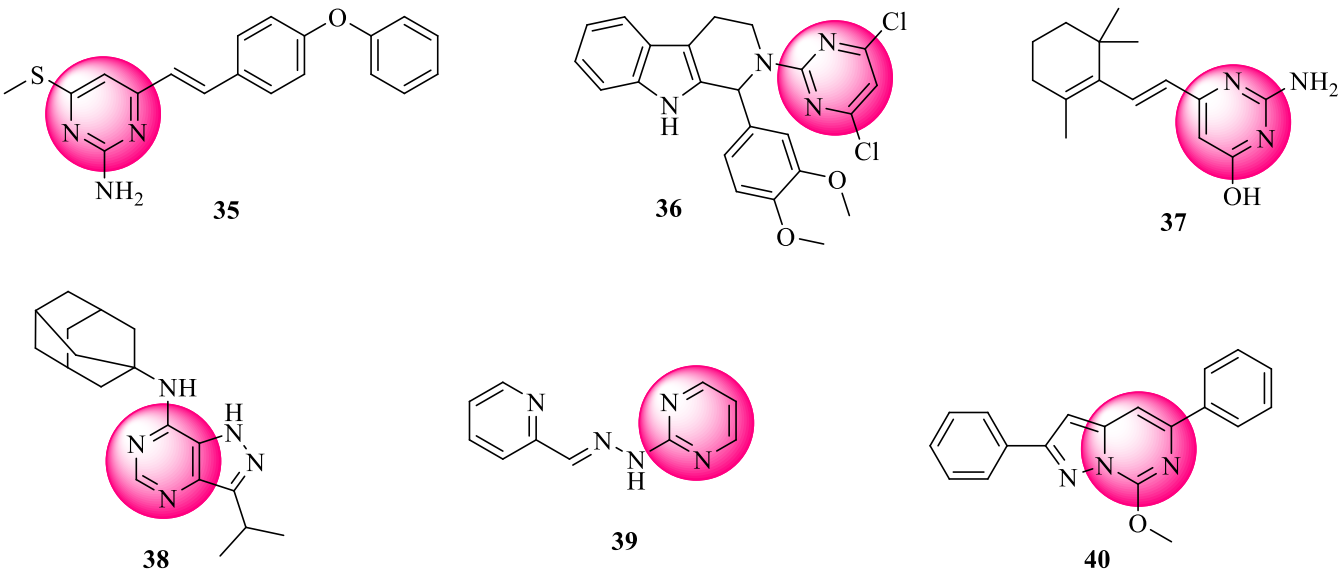



Structure of pyrimidine based anti-inflammatory agents

that of clinically used selective COX-2 inhibitor celecoxib ($IC_{50}$ = 0.78 μM). Compound **11** also displayed more than 2- and 8-folds superior COX-1/COX-2 selectivity index than diclofenac and celecoxib. Compound **12** also exhibited good anti-inflammatory response during *in vivo* cotton pallet granuloma model in rats. Similarly, a series of thiazolidinone linked pyrazolo[4,3-*d*]pyrimidine derivatives was also synthesized by Tageldin *et al.* [85]. The anti-inflammatory potential of these compounds was evaluated using *in vitro* and *in vivo* assay methods. Compound **13** and **14** were reported to have 7- and 10-folds superior COX-2 selectivity than standard drug celecoxib and diclofenac. These compounds did not display any sign of gastrointestinal injury during *in vivo* animal studies. One pot facile synthesis of pyrazolo [3,4-*d*]pyrimido[1,2-*a*]pyrimidine derivatives as potent anti-inflammatory agents was reported by Patil *et al.* [86]. Compounds **15** and **16** from this series had shown 80 % and 86% reduction in carrageenan induced rat paw edema at a dose of 20 mg/kg, respectively. The anti-inflammatory potential of these two compounds was found comparable to that of diclofenac sodium. Tozkoparan *et al.* [87] reported synthesis of thiazolo[3,2-*a*]pyrimidine derivatives as anti-inflammatory agents. Two compounds **17** and **18** displayed superior inflammation inhibitory potential (41% and 38%, respectively) than indomethacin (32%) at a dose of 100 mg/kg, during *in vivo* carrageenan induced rat paw edema assay.

Ashour *et al.* [88] reported the synthesis of fused thieno-pyrimido-triazine and thieno-triazolo-pyrimidine derivatives as analgesic and anti-inflammatory agents. Thieno-triazolo-pyrimidine derivatives displayed superior anti-inflammatory activity than thieno-pyrimido-triazine derivatives. Compounds **19**, **20** and **21** exhibited comparable to superior inflammation inhibition profile in sub-acute formalin induced rat paw edema assay on first day. However, compound **20** (40% inhibition) and **21** (37% inhibition) proved their potent anti-inflammatory activity comparable to diclofenac (40% inhibition) during 8-days study protocol. 2,4,6-Trisubstituted pyrimidine derivatives were synthesized and screened for their anti-inflammatory potency by Yejella & Atla [89]. Two compounds **22** and **23** displayed 62.5% and 65.2% inhibition in carrageenan rat paw edema after 3 h of orally administration of test compounds at a dose of 20 mg/kg. Selective COX-2 inhibitors possessing imidazo[1,2-*a*]pyrimidine nucleus were synthesized by Zhou *et al.* [90]. Compound **24** displayed superior anti-inflammatory activity (63.8%) than standard drug ibuprofen (44.3%) with COX-2 inhibition potential ($IC_{50}$) of 13 μmol/L and selectivity index greater than 13. Gondkar *et al.* [91] reported the good to moderate anti-inflammatory profile of small tetrahydro-pyrimidine derivatives using protein denaturation assay. Among the synthesized compounds five compounds demonstrated greater than 90% reduction in protein denaturation. Compounds **25**, **26**, **27**, **28** and **29** displayed 98%, 97%, 90%, 94% and 96% reduction in protein denaturation, respectively. Novel sulphonamide-based pyrimidine derivatives are also reported in the literature [92]. Two of its compounds **30** and **31** had exhibited comparable to superior TNF-α, IL-6 inhibition potential than dexamethasone with 78%, 96% and 71%, 90%, respectively at 10 μM, respectively. Three novel pyrrolo[2,3-*d*]pyrimidine derivatives synthesized by Mohamed *et al.* [93] displayed potent anti-inflammatory potential than ibuprofen. Compounds **32**, **33**, **34** expressed 73.9%, 95.5% and 95.9% reduction in carrageenan-induced rat paw inflammation after 3 h of treatment, which was found superior than treatment of ibuprofen (60.6% inhibition). Pyrimidine based compound **34** reported by Sondhi *et al.* [94], demonstrated inflammation inhibiting profile comparable to that of ibuprofen with 65% inflammation reducing ability at a dose of 100 mg/kg.

**Antileishmanial activity:** Diversely substituted pyrimidine derivatives as potent antileishmanial agent was synthesized by Suryawanshi *et al.* [95]. All the compounds from this series exhibited superior and potent antileishmanial activity against *Leishmania donovani* than standard drug sodium stibogluconate and miltefosine. The most active compound **35** elicited $IC_{50}$ value of 2.0 μM against intracellular amastigotes of *L. donovani* during *in vitro* studies with selectivity index of 188. Mitefosine and sodium stibogluconate exhibited $IC_{50}$ values of 12.5 μM and 59.8 μM, with selectivity index of 4 and




Structure of pyrimidine based antileishmanial agents

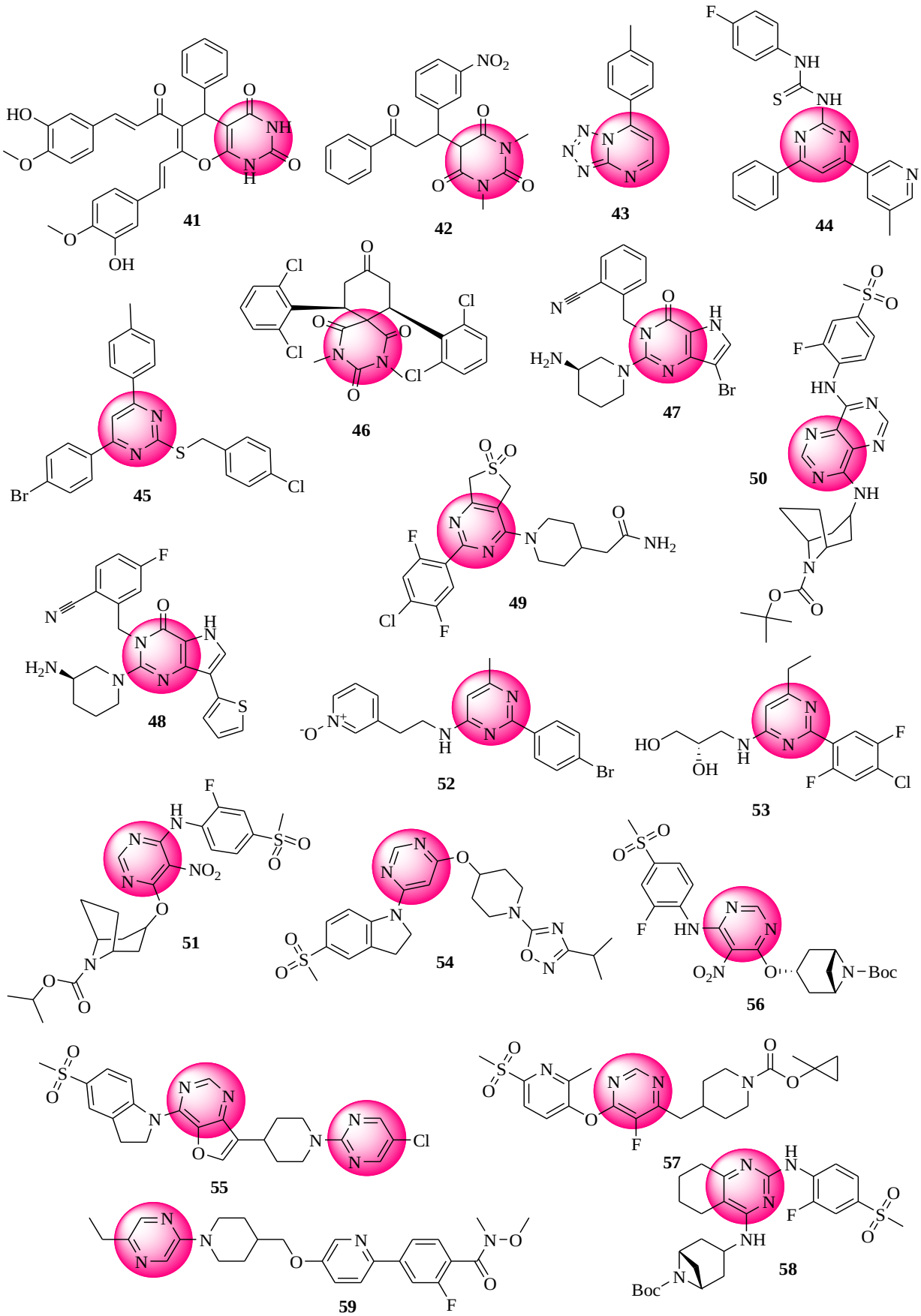
7, respectively. Another hybrid compound containing pyrimidine and β-carboline derivative **36** were synthesized and evaluated for *in vitro* antileishmaninal activity against *L. donovani* [96]. Compound **36** inhibited *L. donovani* amastigotes with $IC_{50}$ value of 1.93 μg/mL. Similarly, terpenyl pyrimidine derivatives **37** was synthesized by Pandey *et al.* [97]. This compound exhibited most promising antileishmanial activity against *L. donovani* amastigotes in Golden hamster model. It had shown 22% and 63% reduction in parasitic infection on 7$^{th}$ and 22$^{nd}$ day of treatment. Jorda *et al.* [98] reported the antileishmanial activity of some disubstituted purines and their structurally similar pyrazolo[4,3-*d*]pyrimidines. The most active compound **38** exhibited $EC_{50}$ value of 1.22 μM against *L. donovani* axenic amastigotes.

Several pyrimidine hydrazones were synthesized and reported by Coimbra *et al.* [99]. Compound **39** had demonstrated attractive antileishmanial profile with $IC_{50}$ value of 9.66 μM, 4.07 μM against promastigote and amastigotes of *L. donovani*, respectively. Atta *et al.* [100] had also synthesized a series of pyrazolo[1,5-*c*]pyrimidine hybrids as potent antileishmanial agents [100]. The most active compound **40** displayed 6-folds and 5.5-folds superior potency against promastigote and amastigote forms of *L. donovani* than standard miltefosine. Compound **40** exhibited $IC_{50}$ value of 1.1 μM, 1.96 μM against *L. donovani* promastigote and amastigote forms, respectively.

**Antidiabetic agent:** A series of curcumin-fused pyrimidine hybrid compounds were synthesized by Yousefi *et al.* [101]. Compound **41** was emerged as competitive inhibitor and inhibited yeast α-glucosidase enzyme with $IC_{50}$ value of 9.7 μM. Similarly, pyrimidine-2,4,6-trione based derivative **42** was synthesized by Barkat *et al.* [102] and documented to have allow yeast α-glucosidase enzyme inhibition potential. Suresh *et al.* [103] had too synthesized and evaluated tetrazolo[1,5-*a*] pyrimidine derivatives as antidiabetic agents but these analogues **43** expressed weak activity than standard drug. Rehman *et al.* [104] had synthesized a series of pyrimidine-thiourea derivatives as potent α-glucosidase inhibitors. Most active compound **44** from this series inhibited yeast α-glucosidase enzyme ($IC_{50}$) at 22.46 μM that was found superior to that of standard drug acarbose (38.22 μM). Gong *et al.* [105] had reported synthesis and α-glucosidase inhibitory activity of diarylpyrimidine derivative compound **45**. This compound inhibited yeast α-glucosidase enzyme with $IC_{50}$ value of 19.60 μM, whereas standard drug acarbose produced $IC_{50}$ value of 817.38 μM. Barakat *et al.* [106] had reported dihydropyrimidine as antidiabetic agents targeting α-glucosidase enzyme. The most active compound **46** was documented to have $IC_{50}$ value of 2.46 μM. DPP-4 inhibition activity of pyrrolopyrimidine derivatives were studied by Xie *et al.* [107]. Among the synthesized compounds, the most active compound **47** displayed $IC_{50}$ value of 1.4 nM against DPP-4 enzyme. This compound also inhibits DPP4-8 and DPP-9 isoform. Based on these results, some new pyrrolopyrimidine compounds again designed, synthesized and evaluated against DPP-4 enzyme by Xie *et al.* [108]. An improved DPP-4 inhibition profile was elicited by compound **48** from this series with $IC_{50}$ at 0.76 nM. This compound displayed 28.31% inhibition of DPP-4 enzyme during *in vivo* studies in rats in comparison to trelagliptin displayed 21.75% inhibition at a dose of 3 mg/kg. Fused pyrimidine derivative **49** was documented by Negoro *et al.* [109] with GPR119 agonistic activity. It displayed promising agonistic activity with $EC_{50}$ value of 8.3 nM and strong blood glucose lowering potential at a dose of 0.1 mg/kg in mice model. Nanomolar active potent pyrimido-pyrimidine derivatives were reported as GPR119 agonists by Fang *et al.* [110]. Compound **50** exhibited strongest GPR119 agonistic activity ($EC_{50}$ = 2.2 nM). 5-Nitropyrimidines derivative **51** synthesized by Fang *et al.* [111] displayed nanomolar GPR119 agonistic profile with $EC_{50}$ at 0.06 nM. Several phenylpyrimidine derivatives were structurally optimized and evaluated as GPR119 agonists by Negoro *et al.* [112]. Compound **52** was documented with $EC_{50}$ of 1.2 μM. It also expressed good oral bioavailbility in animal model. Inspired from previous results, Negoro *et al.* [113] also designed and synthesized a new series of phenylpyrimidines. The most potent compound **53** showed good metabolic stability, bioavailability and pharmacokinetic profile with improved GPR119 agonistic activity ($EC_{50}$) of 0.28 μM. It also exhibited strong blood glucose lowering ability (25%) at a dose of 1 mg/kg in mice. Diversely substituted indolinylpyrimidine analogues were synthesized and reported for their potent GPR119 agonistic activity by Sato *et al.* [114]. Compound **54** presented highest agonistic potency with $EC_{50}$ of 7.7 nM.

Koshizawa *et al.* [115] optimized furo[3,2-*d*]pyrimidine nucleus to develop potent GPR119 agonist compounds The most active compound **55** displayed nanomolar activity profile as GPR119 agonist with $EC_{50}$ at 42 nM. Compound **55** was also studied for its anti-hyperglycemic activity in mice model and lowers 33% plasma glucose level when administered orally at a dose of 10 mg/kg. Novel pyrimidine-linked bicyclic compounds as GPR 119 agonists were reported by Yang *et al.* [116]. Compound **56** from this series found most potent derivative with $EC_{50}$ value of 1.2 nM against GPR119 receptor. A nanomolar active dialkoxypyrimidine derivative **57** was synthesized by Buzard *et al.* [117]. Compound **57** displayed potent GPR119 agonistic potency with $EC_{50}$ value of 34 nM and displayed best pharmacokinetic and pharmacodynamic profiles. Several novel fused pyrimidine derivatives were also reported by Fang *et al.* [118]. The most active compound **58** exhibited moderate GPR119 agonist potency with $EC_{50}$ value of 0.27 μM. When administered orally at a dose of 15 mg/kg body weight, compound **58** rapidly lowered the elevated blood glucose level in hyperglycemic rats. Jang *et al.* [119] also synthesized thienopyrimidine based compounds as potent GPR119 agonist activity with $EC_{50}$ value of 77 nM. The most active compound **59** showed good glucose tolerance and reduced blood sugar level in hyperglycemic rats.

**Anti-alzheimer's activity:** Pyrimidine-2,4-diamine derivatives have emerged as potent anti-Alzheimer agents. Mohamed *et al.* [120] reported that the synthesized compound **60** exhibited potent AChE and BuChE inhibition activities with $IC_{50}$ at 9.9 μM and 11.4 μM, respectively. Similarly, 4,6-diphenylpyrimidine scaffold based nanomolar active anticholinesterase (AChE) and monoamine oxidase-A (MAO-A) inhibitors were synthesized by Kumar *et al.* [121]. The most potent compound **61** displayed $IC_{50}$ at 30.46, 0.666 and 18.34



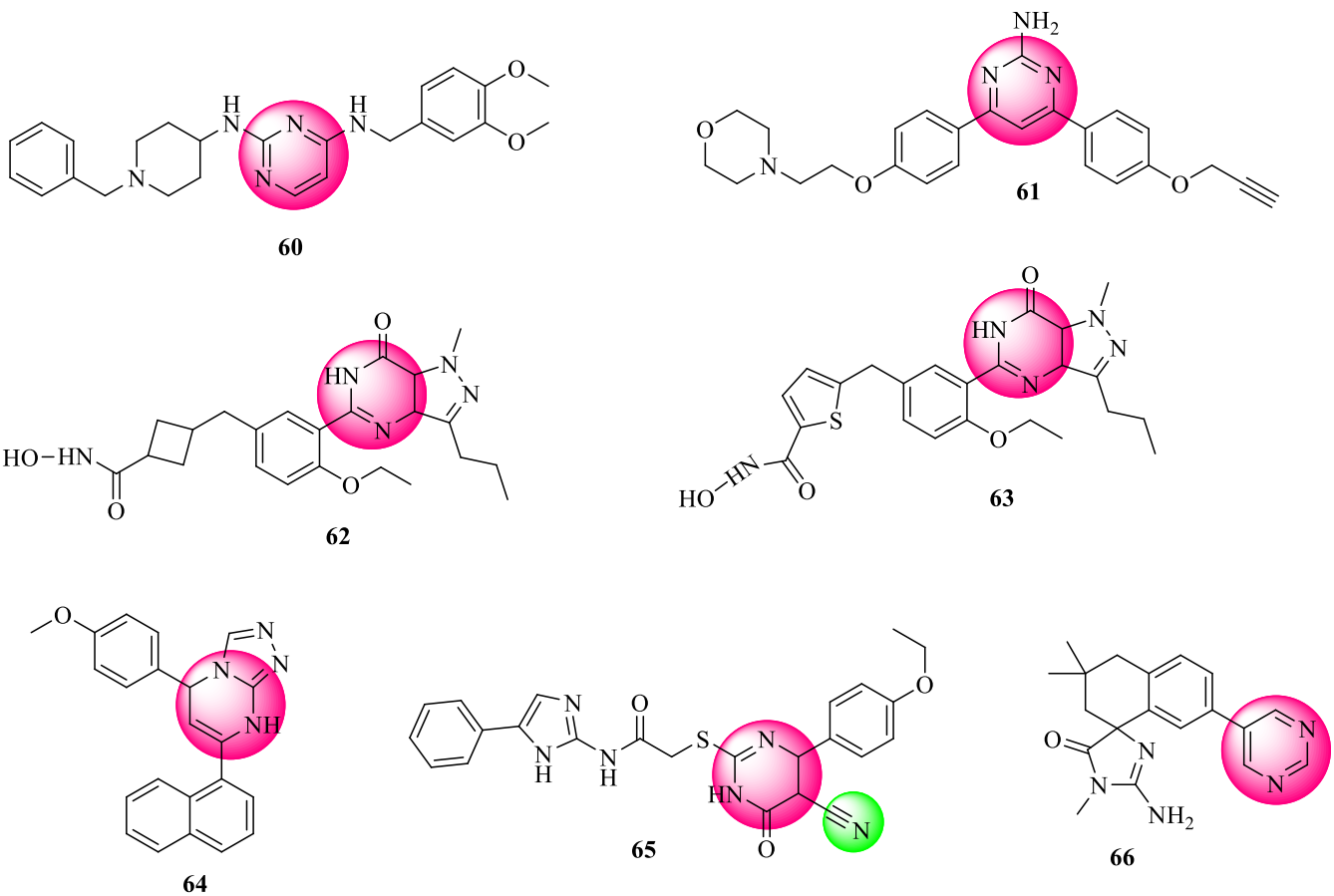
Structure of pyrimidine based antidiabetic agents

nM against AChE, butrylcholinesterase and MAO-A enzymes, respectively.

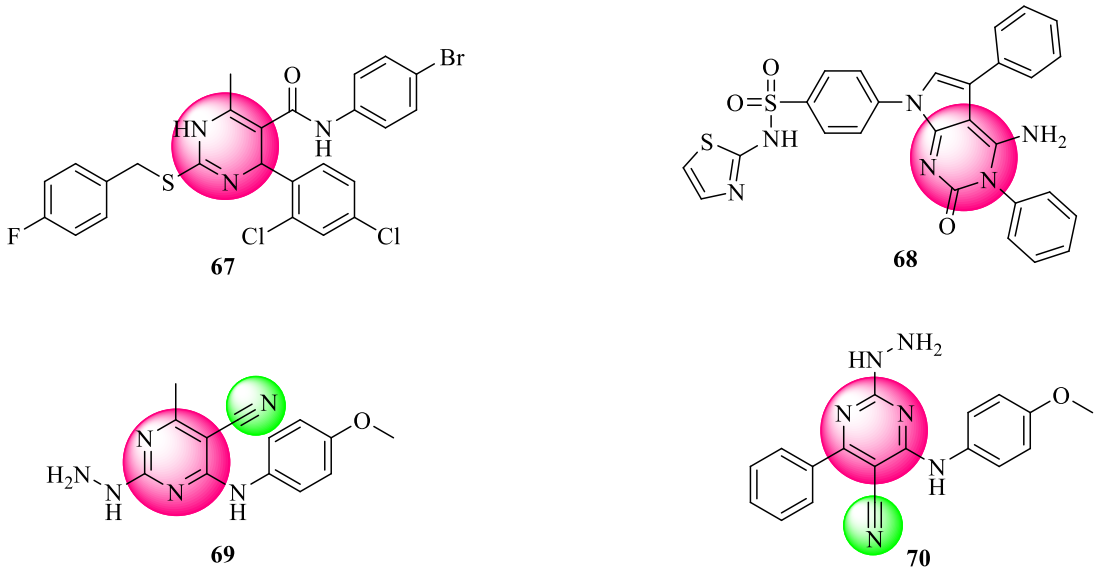
Some sildenafil based hydroxamic acid derivatives were synthesized as phosphodiesterase-5 inhibitors for the treatment of Alzheimer's disease. The most potent compound **62** inhibited the PDE5 activity with $IC_{50}$ value at 60 nM [122]. Another compound **63** sharing same template inhibited PDE5 enzyme with $IC_{50}$ of 15 nM, but this compound was not active during *in vivo* studies [123]. Naphthalene-triazolopyrimidine based hybrid series was reported by Umar *et al.* [124]. The most active compound **64** displayed lowest $IC_{50}$ value of 8.6 and 150 nM against AChE and BuChE, respectively. It was found more potent than standard drug donepezil ($IC_{50}$ 49 nM). These molecules also exhibited superior amyloid β-self aggregation inhibition potential than standard drug curcumin in animal model. Yan *et al.* [125] had synthesized pyrimidine linked thioacetamide derivatives as β-site amyloid precursor protein cleaving enzyme 1 (BACHE1) inhibitors. Compound **65** exhibited potent BACHE1 inhibition with $IC_{50}$ value of 4.6 μM. It exhibited good blood brain permeability with low cytotoxicity against normal human neurons. Pyrimidine derivative **66** synthesized by Hunt *et al.* [126] and optimized to yield potent BACHE1 inhibitors.

**Antihypertensive activity:** Several 1,4-dihydro-5-pyrimidine carboxamide analogues as antihypertensive candidates were synthesized by Alam *et al.* [127]. Most of the compounds exhibit their superior antihypertensive activity than nifedipine. The most active compound **67** significantly reduces the blood pressure within 15 min of drug administration and exerted its antihypertensive activity up to 15 h. Katouah & Gaffer [128] synthesized benzene sulfonamide substituted pyrrolo-[2,3-*d*]pyrimidines for their antihypertensive potential. All the synthesized derivatives displayed potent antihypertensive activity than prazosin. The most active compound **68** containing thiazol moiety displayed superior activity than other derivatives. Diversely substituted achiral pyrimidine-based compounds were synthesized and evaluated for their anti-hypertensive activity on rabbits by Farghaly *et al.* [129]. Two most active compounds **69** and **70** reduced the arteries tension by 89.2% in comparison to nifedipine (57.6%).

**Anticonvulsant activity:** Shaquiquzzaman *et al.* [130] synthesized novel Schiff bases of pyrimidine carbonitrile derivatives as anticonvulsant agents. These derivatives exhibited no sign of neurotoxicity up to oral dose of 300 mg/kg in rats. The most active compound **71** from the above series displayed superior anticonvulsant activity than phenytoin during maximal electroshock (MES) induced convulsions in mice model. Diphenylpyrimidine semicarbazones were synthesized by Alam *et al.* [131] and their anticonvulsant activities was evaluated using maximal electroshock (MES) and subcutaneous pentylenetetrazole (*sc*PTZ) assay methods. The most active compound **72** exhibited attractive anticonvulsant protection at a dose of 30 mg/kg for short period as well as at 100 mg/kg dose for long period of time. It also demonstrated no sign of



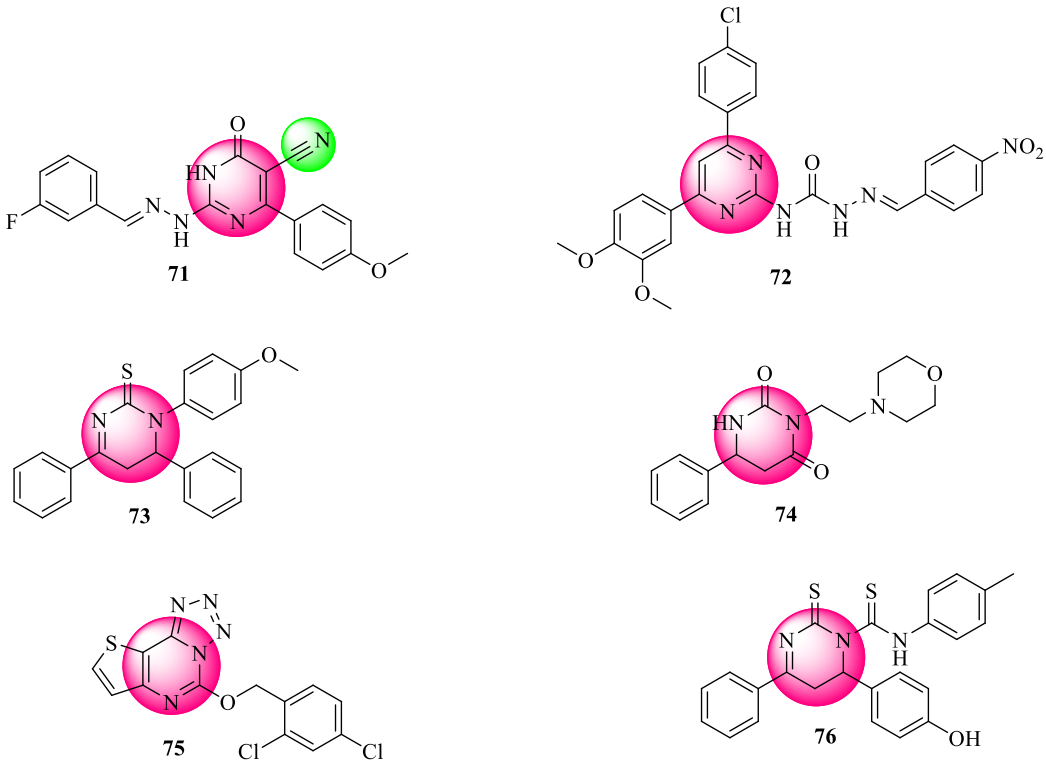

Structure of pyrimidine based anti-alzheimer's agents




Structure of pyrimidine based antihypertensive agents

neurotoxicity at both dose levels. An anticonvulsant series of 5,6-dihydropyrimidine-2(1*H*)-thione derivatives were synthesized and reported as γ-aminobutyric acid aminotransferase (GABA-AT) inhibitors by Sahu *et al.* [132]. Compound **73** exhibited good protection against maximal electroshock (MES) and subcutaneous pentylenetetrazole (*sc*PTZ) induced convulsions in mice. It also inhibited the GABA-AT enzyme activity with $IC_{50}$ at 18.42 μM, found more 2-fold superior than Vigabatrin (41.21 μM). Compound **73** documented with median effective dose ($ED_{50}$) and median toxic dose ($TD_{50}$) of 16.8 mg/kg (MES) 378.2 mg/kg (*sc*PTZ) and 534.4 mg/kg, respectively.

Hexahydro-pyrimidine analogues were synthesized and also studied for their anticonvulsant potential using MES mice model [133]. Only one compound **74** displayed anticonvulsant activity and no sign of neurotoxicty at a dose of 300 mg/kg. Wang *et al.* [134] reported antidepressant and anticonvulsant activity of thieno[2,3-*e*]pyrimidine derivatives, where compound **75** displayed quite promising antidepressant activity without effecting locomotor activity. Pyrimidine carbothio-




Structure of pyrimidine based antihypertensive agents

amide derivative **76** was synthesized by Sahu *et al.* [135] as potent GABA-AT inhibitor with inhibitory potency of 12.23 μM. This compound exhibited median effective dose ($ED_{50}$) and median toxic dose of 15.6 mg/kg (MES), 278.4 mg/kg (*sc*PTZ) and 534.4 mg/kg, respectively.

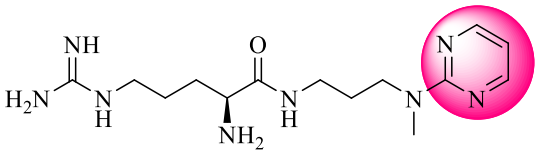
**Antimicrobial activity:** Arginine-linked pyrimidine derivatives were synthesized and evaluated using *in vitro* and *in vivo* antimicrobial assay methods by Haebich *et al.* [136]. Compounds **77** and **78** derivatives exhibited no antibacterial activity during *in vitro* screening but provided strong activity during *in vivo* studies in mice against various lethal pathogenic bacterial infections caused by *Staphylococcus aureus* and *Escherichia coli* at a dose of 30 mg/kg through intraperitoneal (i.p.) route. Survival rate of infected mice was increased up to 80% when treated with these compounds. Both of these compounds exhibited no sign of toxicity up to maximum dose of 450 mg/kg (*i.p.*). Pyrimidine derivatives synthesized by Raj *et al.* [137] exhibited good to moderate antibacterial and antifungal activities. Most potent compound **79** displayed superior antifungal activity with minimum inhibitory concentration (MIC) value of 28 μg/mL against *Candida albicans*, which was found comparable to fluconazole. Al-Neyadi *et al.* [138] too synthesized substituted pyrimidine derivatives as antimicrobial agents. Most potent compound **80** inhibited the growth of *E. coli* and *Pseudomonas aeruginosa* with MIC of 9.0 μg/mL.

Phenylthiazole linked pyrimidine derivatives were synthesized by Kotb *et al.* [139]. Among the synthesized derivatives, compounds **81** and **82** exhibited potent antimicrobial activity against methicillin-resistant *S. aureus* with MIC less than 0.8 μg/mL. These compounds were also active against vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* bacteria. 2,4,5-Trisubstituted pyrimidine derivative **83** developed by Al-Neyadi *et al.* [138] exhibited MIC value of 1.0 μg/mL against *E. coli*. 1,3,4-Oxadiazole pyrimidine derivatives as potent antimicrobial agents targeting pyruvate dehydrogenase multienzyme complex E1 (PDHc-E1) inhibitors were synthesized by He *et al.* [140]. Compound **84** inhibited *E. coli* PDH-E1 enzyme with $IC_{50}$ value of 0.97 μM and inhibited cyanobacteria with $ED_{50}$ value of 0.83 μM. In continuation of this success, Ha *et al.* [141] had further synthesized compound **85** with tremendous *E. coli* PDHc-E1 enzyme inhibition potency ($IC_{50}$) of 0.15 μM. Pyrimidine and 1,3-oxazolidone hybrids were synthesized by Romeo *et al.* [142] and found that compounds **86** and **87** had shown strong antibacterial potency against Gram-positive bacteria then Gram-negative ones. These compounds inhibited growth of *B. subtilis* and *S. aureus* with MIC values ranges from 2.8-3.2 μg/mL and 4.2-4.8 μg/mL, respectively. The antibacterial activities of these agents are superior than the standard drug ciprofloxacin.

Ibrahim [143] reported the synthesis of novel substituted pyrimidine-thiophene derivatives and found that compound **88** exhibited potent antifungal activity. Yi *et al.* [144] reported novel type of pyrimidine linked pleuromutilin derivatives exhibiting the potent antibacterial activity against *B. subtilis*, *E. coli*, MRSA and methicillin resistant *Staphylococcus epidermidis* (MRSE) at 0.125-0.25 μg/mL (MIC). These compounds exerted superior antimicrobial activity than tiamulin fumarate. Fang *et al.* [145] reported the strong antibacterial activity against vancomycin-resistant Enterococcus (VRE) and MRSA based on thiophene-pyrimidine hybrids. Two compounds **89** and **90** inhibited growth of *S. aureus*, *S. epidermidis*, *B. subtilis* and *E. faecalis* at MIC of 2 μg/mL. Nagarajan *et al.* [146] documented the synthesis of 2-aminopyrimidine nucleus based antibacterial agents against *K. pneumoniae*, *E. coli* and *S. aureus*. Compounds **91** and **92** were found most active among the synthesized derivatives. Similarly, diversely substituted pyrimidine derivative **93** inhibited *Stenotrophomonas maltophilia* at 2 μg/mL (MIC) as reported by Chen *et al.* [147]. Symmetrical pyrimidine analogues were reported by Fadda *et al.* [148] as potent antibacterial agent and found that compound **94** emerged as broad-spectrum antimicrobial agent that exhibited MIC of 3.12 μg/mL and has twice potent that standard drug cephalothin (6.25 μg/mL). Compounds **95** and **96** were synthesized by Kayathi *et al.* [149] and both were equipotent like chloramphenicol and ketoconazole against pathogenic fungi *Aspergillus niger*. Furthermore, promising results of antimicrobial agents based on hybrid pyrimidine-carbonitrile derivatives were reported by Deshmukh *et al.* [150]. Compound **97** displayed the highest activity against *S. aureus*.

Imidazole linked pyrimidone and pyrimidinethione derivatives were synthesized by Fadda *et al.* [151], where compound **98** inhibit Gram-positive bacteria (*S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli*) while pyrimidine-thione derivative **99** exhibited strong inhibition potential against Gram-negative bacteria and fungi. Compounds **100** and **101** based on pyrrolo-[2,3-*d*]pyrimidine analogues demonstrated higher zone of inhibition than standard drugs (ampicillin and tetracyclin) against different strains of bacteria and fungi as reported by Hilmy *et al.* [152]. Fused pyrimidine derivatives displayed promising and broad-spectrum antimicrobial activity [153], for example, pyrrolopyrimidine and pleuromutilin hybrids were designed and synthesized to enhance the antibacterial potency of pleuromutilin [154]. Compound **102** exhibited highest antibacterial potency against MRSA, *S. aureus*, *B. subtilis*, *E. coli* with MIC values of 0.125 μg/mL, 0.0625 μg/mL, 1 μg/mL and 4 μg/mL, respectively. This compound also rapidly killed MRSA in mice model than valnemulin.

Several imidazopyrimidine compounds under three different reaction schemes were synthesized by Al-Tel *et al.* [155] as broad-spectrum antimicrobial agents. Three most active compounds **105**, **106** and **107** displayed MIC ranges from 0.64 μg/mL to 2.85 μg/mL. Pyrazolopyrimidine derivatives **108-112** developed by Bakavoli *et al.* [156] displayed strong antimicrobial profile comparable to streptomycin. Compound **113** inhibited growth of *B. subtilis*, *S. aureus*, *E. coli* and *P. aeruginosa* with MIC value of 3.90 μg/mL, 7.81 μg/mL, 15.62 μg/mL and 7.81 μg/mL, respectively. This derivative was reported to have superior antimicrobial potency than tetracycline. Another novel two pyrazolopyrimidine derivatives (**114** and **115**) with their potent antimicrobial properties were reported by Rostamizadeh *et al.* [157]. Both compounds **114** and **115** were found two times more potent than penicillin G against *S. aureus* and *E. raffinosus* with MIC value of 3.8 μg/mL and 4.2 μg/mL; 12.3 μg/mL and 14.2 μg/mL, respect-



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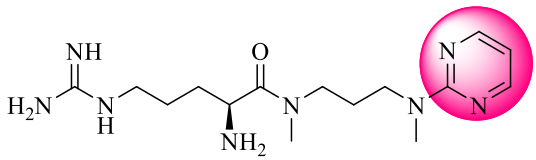

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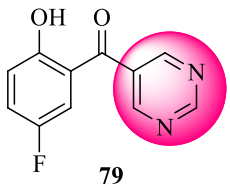

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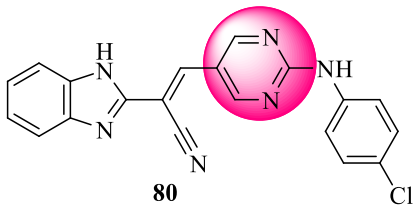

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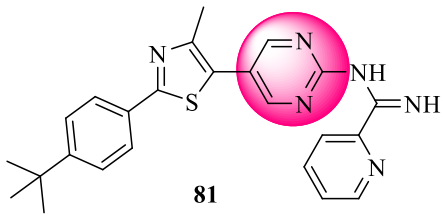

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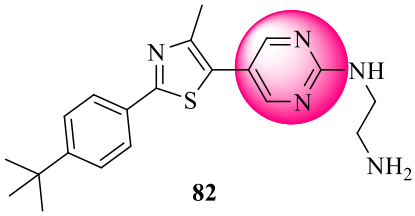

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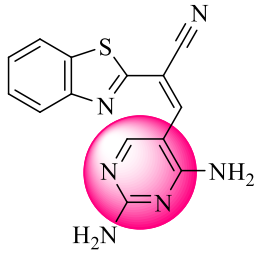

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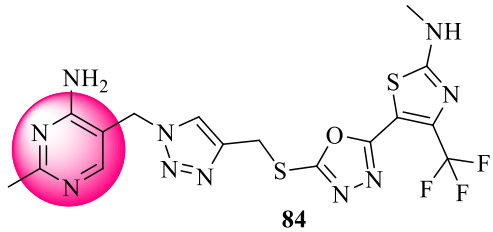

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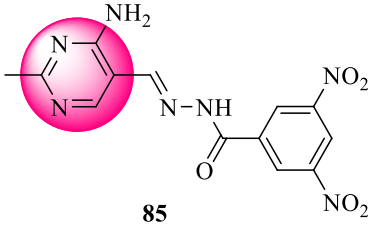

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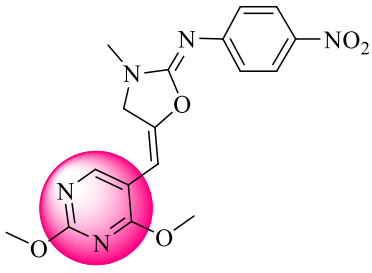

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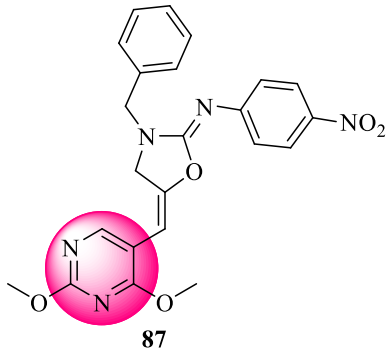

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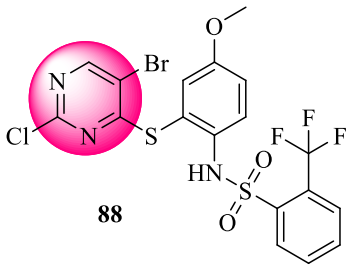

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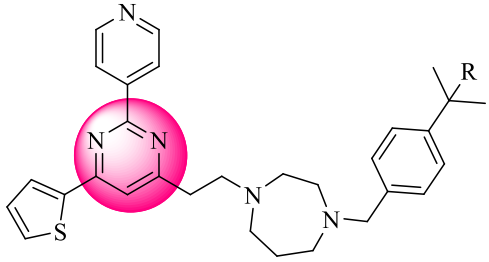
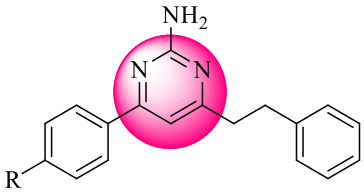
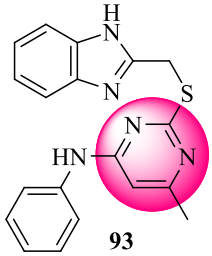


89 R= H
90 R = $CH_3$



91 R= F
92 R = $OCH_3$



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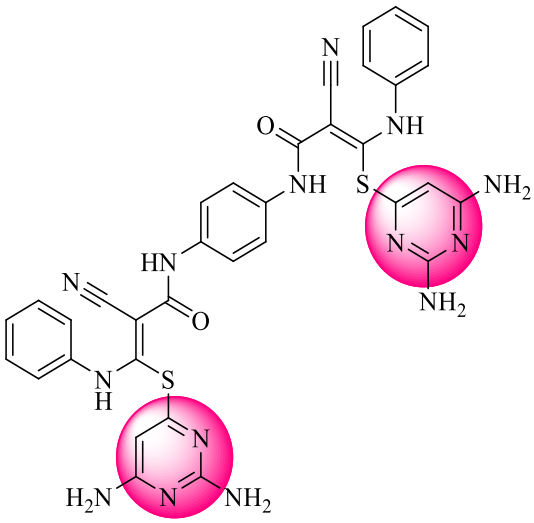

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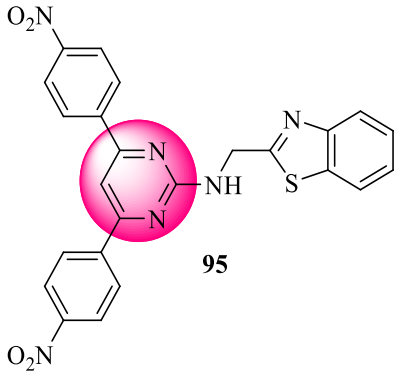

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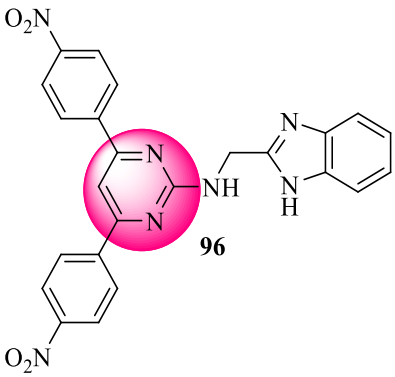

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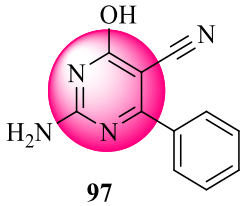

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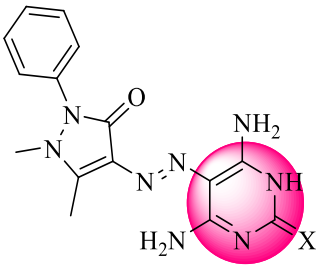
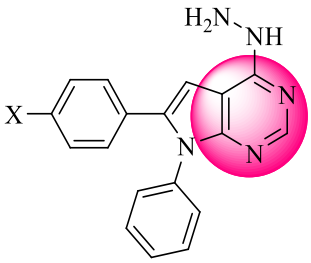
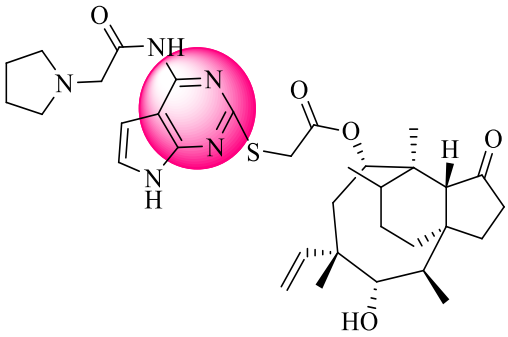


**98 R=O**
**99 R=S**



**100 R=H**
**101 R=F**



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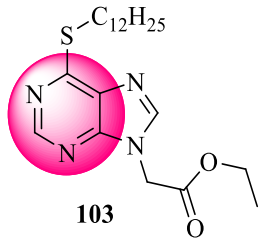

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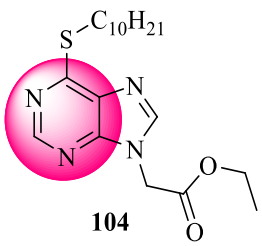

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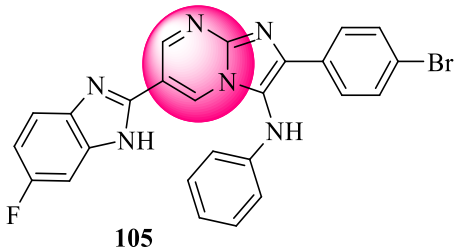

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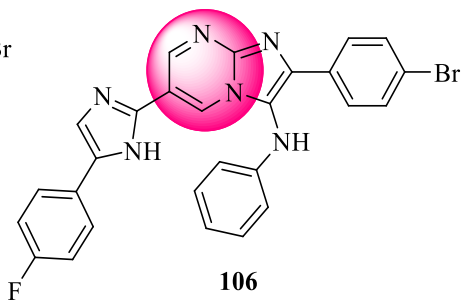

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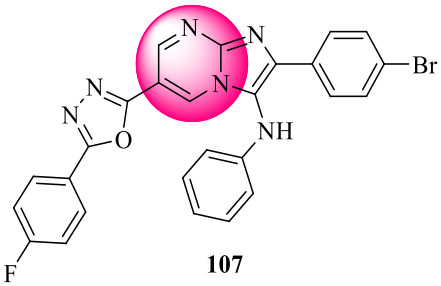

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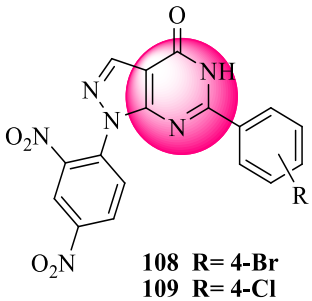
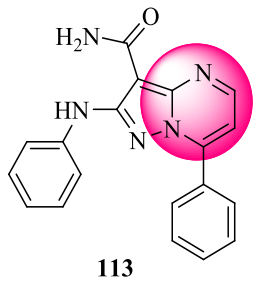


**108 R= 4-Br**
**109 R= 4-Cl**
**110 R= 3-$NO_2$**
**111 R= 3-OH**
**112 R= 2-OH**



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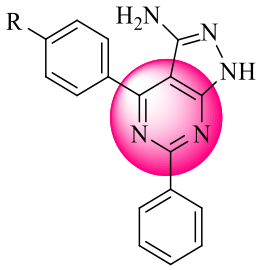
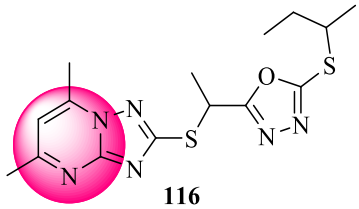


**114 R= Br**
**115 R= $OCH_3$**



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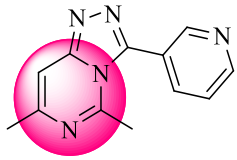

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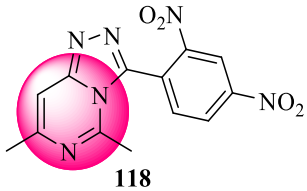

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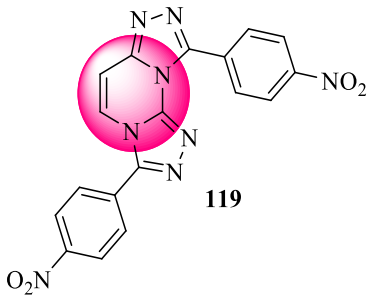

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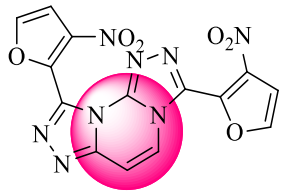

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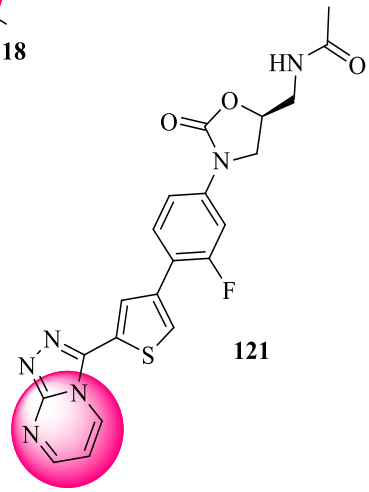

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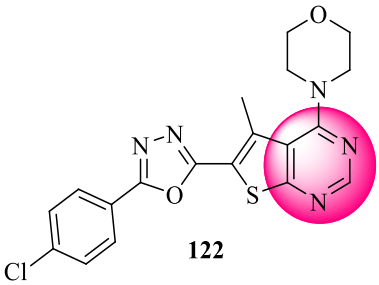

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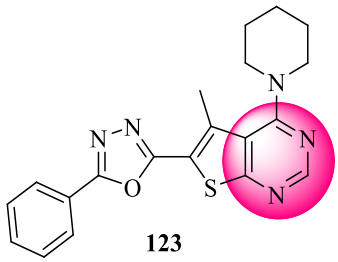

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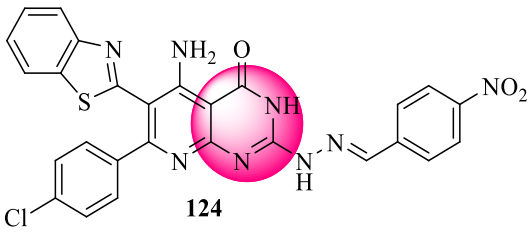

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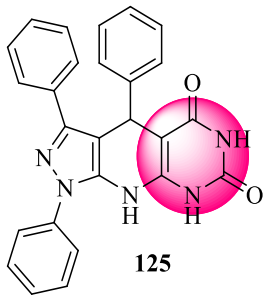

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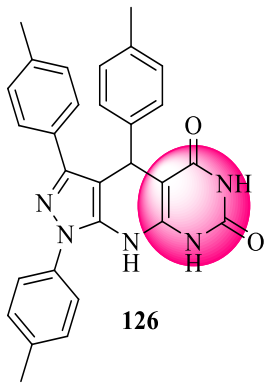

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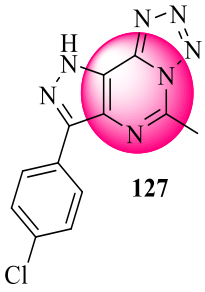

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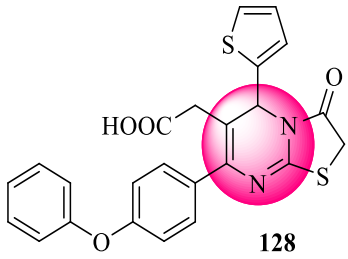

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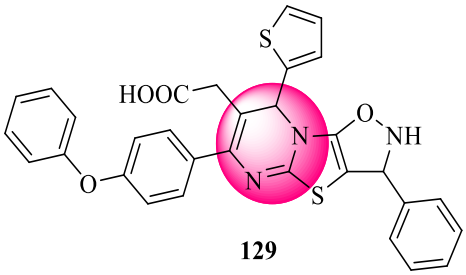

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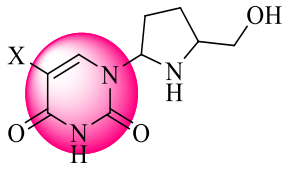
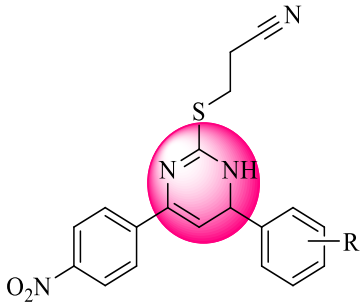
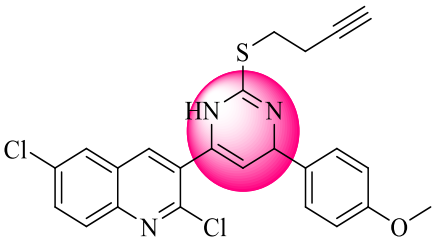


**130 R= Br**
**131 R= Cl**



**132 R= 2-Cl**
**133 R= 2-$NO_2$**
**134 R= 2-OH**
**135 R= 3-$OCH_3$ 4-OH**
**136 R= 3-$NO_2$**



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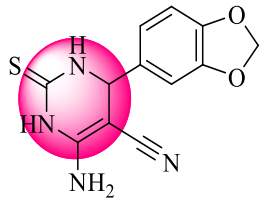

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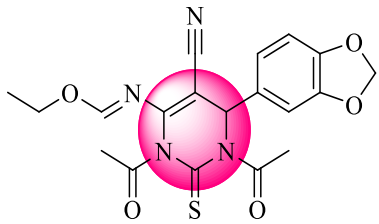

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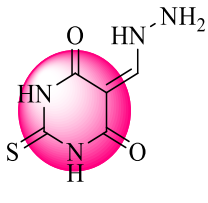

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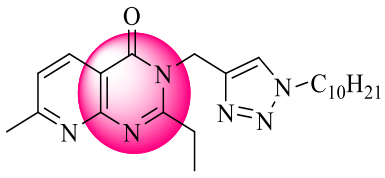

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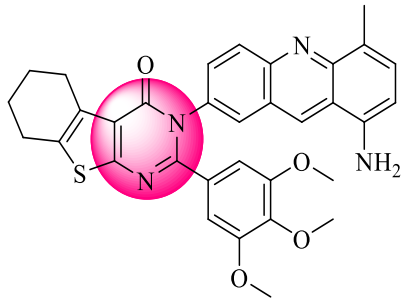

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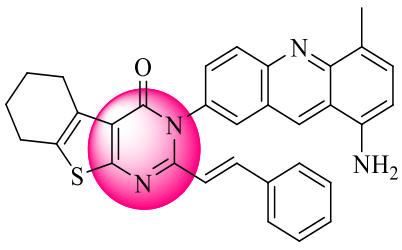

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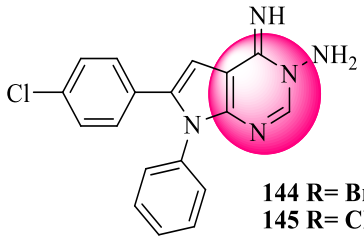
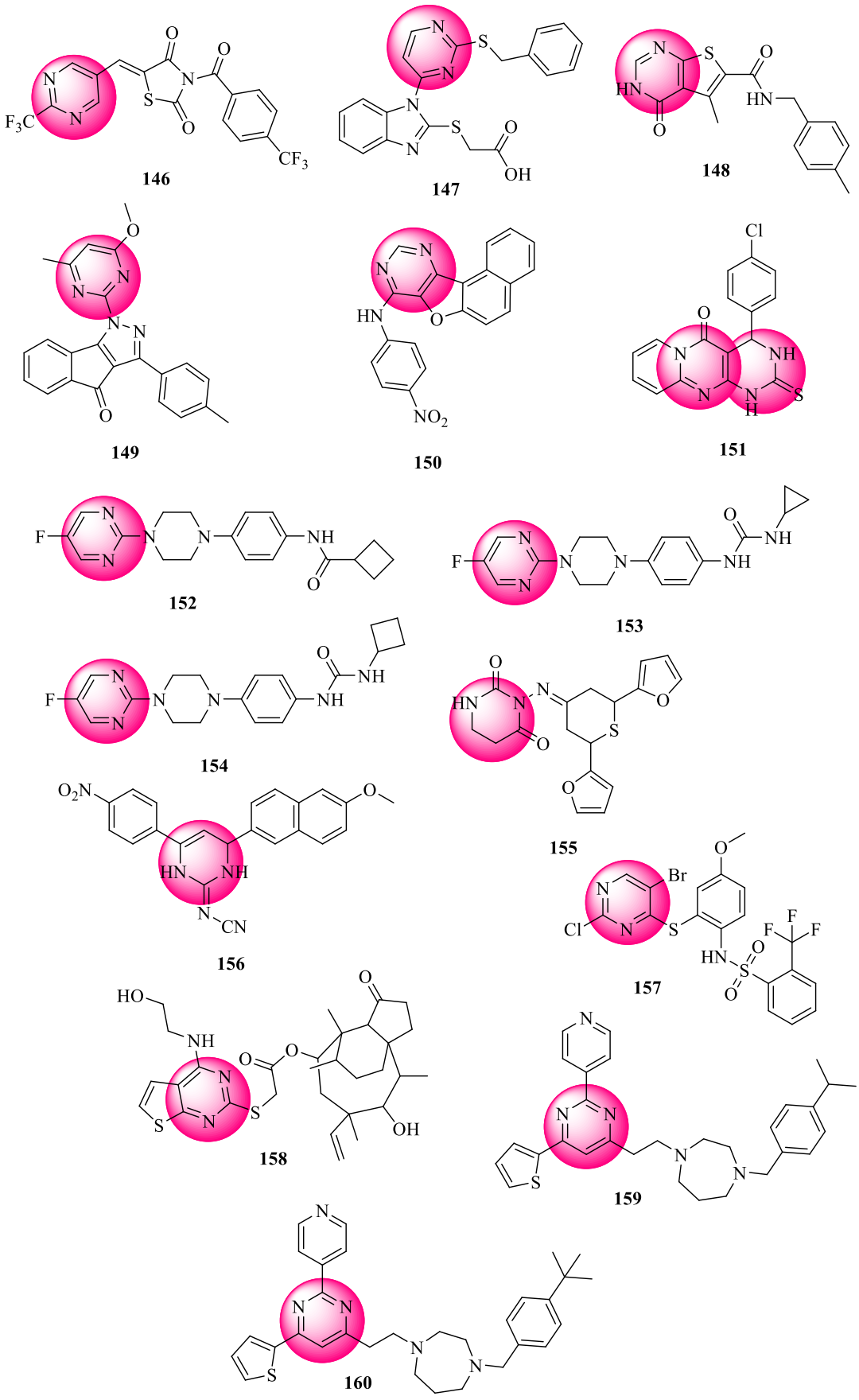


**144 R= Br**
**145 R= Cl**




Structure of pyrimidine based antimicrobial agents

tively. Another type of hybrid compound, triazolopyrimidine linked 1,3,4-oxadiazole derivative **116** synthesized by Liu *et al.* [158] displayed $EC_{50}$ at 3.34 μg/mL. Kumar *et al.* [159] also reported triazolopyrimidine derivatives **117** and **118** as potent antibacterial agents. These compounds displayed superior potency than standard drugs chloramphenicol and streptomycin.

Using pyrimidine-centered tricyclic structure as novel scaffold, Prakash *et al.* [160] synthesized compounds **119** and **120** and found to have two- to eight-fold superior antimicrobial potency than cefaclor and linezolid against *B. subtilis*, *Salmonella typhi*, *S. aureus*, *E. coli* and *S. epidermidis*. Khera *et al.* [161] synthesized triazolo[4,3-*a*]pyrimidine clubbed oxazolidinone derivatives as bacterial ribosomal 50S inhibitor. Among the synthesized compounds in this series, compound **121** exhibited strong antimicrobial potential with MIC 4- to 16-folds superior than standard drug linezolid. Triloknadh *et al.* [162] also synthesized similar compounds **122** and **123** that exhibited antibacterial activity superior than gentamicin. Pyridopyrimidine based compounds reported by Yalagala *et al.* [163] exhibited broad spectrum antibacterial activity. Compound **124** exhibited strong antibacterial and antifungal activities similar to ciprofloxacin and clotrimazole. Moreover, Bazgir *et al.* [164] had reported fused pyrimidine ring derivative **125** and **126** with MIC value less than 2 μg/mL against a panel of bacterial strains. Pyrazole-pyrimidine hybrids as antibacterial agents were reported by Hafez *et al.* [165], where compound **127** was active against both the Gram-positive and Gram-negative bacterial strains. Behalo [166] carried out synthesis of pyrimidine linked thazole and isoxazole derivatives. Compounds **128** and **129** exhibited excellent antibacterial and antifungal potential similar to streptomycin and ketoconazole. The thiazolidine-pyrimidine hybrid compounds **130** and **131** synthesized by Sriharsha *et al.* [167] reported the superior antibacterial activity than ciprofloxacin against *Salmonella typhi*. 1,6-Dihydropyrimidine nucleus containing compound **132**, **133**, **134**, **135** and **136** also exhibited broad spectrum antibacterial and antifungal activities and were found equipotent to that of standards chloramphenicol and ketoconazole [168]. Broad spectrum antibacterial along with potent antitubercular activity was reported with compound **137** [169]. This compound also exhibited low cytotoxicity against normal human cells. Mourad *et al.* [170] carried out synthesis of pyrimidine-5-carbonitrile derivatives as antibacterial agents. Potent antibacterial activities were recorded for compound **138** found comparable to norfloxacin. Pyrimidine hydrzide derivative **139** synthesized by Aly *et al.* [171] also exhibited excellent antibacterial and antifungal activities.

Synthesis of long alkyl side chain containing pyrido[2,3-*d*]-pyrimidine derivatives as antibacterial agents were reported by Kumar *et al.* [172] and found that compound **140** exhibited superior antibacterial activity against *P. aeruginosa*, *S. pneumonia* and *K. pneumonia*. Moreover, tricyclic fused pyrimidine scaffold was explored by Abbas *et al.* [173] to design potent antibacterial compounds **141** and **142**. Further, pyrimido[4,5-*b*]-quinolone-based compounds were designed by Abbas *et al.* [174]. The most active compound **143** from this series displayed antibacterial and antifungal activities comparable to that of nalidixic acid. Hilmy *et al.* [152] synthesized dihydropyrrolopyrimidines derivatives **144** and **145** and exhibited potent antibacterial activity against *S. aureus*. Similarly, Raghu *et al.* [175] evaluated and reported thiazolidinedione linked pyrimidine analogues as broad-spectrum antimicrobial and anti-tubercular agents. Compound **146** was reported as the most potent derivative having 6.4-folds superior potency against methicillin-resistant *S. aureus* than the standard drug linezolid with MIC value of 10.8 μM. It also exhibited 1.85-folds superior potency against *S. aureus* than the standard drug streptomycin with MIC value of 6.4 μM. Benzimidazole linked pyrimidine hybrids were synthesized by Basha & Akshay [176] and found that compound **147** displayed potent and attractive antimicrobial activity against *E. coli* at 6.5 μM, which was found comparable to the clinically used drug gentamycin. Vlasov *et al.* [177] synthesized benzylcarboxamide substituted pyrimidine derivatives and found that those compounds having small electron donating fragments such as methyl and methoxy groups at *p*-position and with no substitution on benzene ring were found more active than compounds having substitution on *ortho*- and *meta*-positions of benzene ring. These compounds displayed the highest inhibition potential against *S. aureus* and *B. subtilis*. Compound **148** exhibited zone of inhibition of 23 mm, 20 mm, 21 mm, 21 mm, 23 mm and 17 mm against *S. aureus*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, *B. subtilis and C. albicans*, respectively.

Mor *et al.* [178] designed and synthesized novel pyrazalone pendent pyrimidine derivative (compound **149**) as promising antibacterial and antifungal agent against *R. oryzae*, *S. aureus*, *S. typhi*, *E. faecalis* and *E. coli* with MIC value (2 μM to 5 μM) comparable to the clinically used drugs tetracycline and fluconazole. Roopa *et al.* [179] synthesized naphtho[2,1-*b*]-furan fused pyrimidine derivatives and found that compound 1**50** exhibited strongest antibacterial activities against *E. coli* with MIC value of 3.125 μg/mL. Rai *et al.* [180] had reported a three-component expedient synthesis of some pyrido-pyrimidine derivatives and evaluated them against *S. typhemurium*, *S. aureus*, *B. subtilis* and *E. coli*. Compound **151** exhibited highest antibacterial activity against *S. typhemurium* with MIC value of 3.125 μg/mL and displayed zone of inhibition of 23.5 mm. Piperazine linked pyrimidine derivatives were synthesized by Rejinthala *et al.* [181] and screened them against six Gram-positive and Gram-negative bacterial strains which includes *K. pneumonia*, *E. coli*, *E. faecium*, *A. baumannii* and *S. aureus*. Compounds **152**, **153**, **154** displayed strongest antibacterial activity against with MIC value of 27.1 μg/mL, 32.4 μg/mL and 32.4 μg/mL and respectively. Ahmad *et al.* [182] synthesized 2*H*-thiopyran clubbed pyrimidine derivatives and found to be effective against clinical isolates of Gram-positive, Gram-negative bacteria and pathogenic fungal strains. 2,6-Difuran substituted derivative **155** displayed lowest MIC value of 0.25 μg/mL against *C. albicans*.

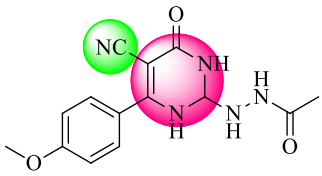
Sivagami *et al.* [183] had developed a multicomponent synthetic protocol for synthesizing naphthalene linked pyrimidine derivatives as potent antimicrobial agents. The most active derivative **156** was capable of inhibiting *K. pneumoniae* with MIC at 28 μg/mL. Mallikarjunaswamy *et al.* [184] reported the synthesis of phenylamine linked substituted pyrimidine derivatives. Among them compound **157** displayed

promising antibacterial and antifungal potential. Ding *et al.* [185] had also reported natural product pleuromutilin fused pyrimidine derivative **158** as potent antibacterial agents against highly pathogenic microbial strains, which includes methicillin resistant *S. aureus, S. agalactiae, E. coli* and *S. aureus* with MIC value at 0.0019 μg/mL, 0.0019 μg/mL, 0.0076 μg/mL and 0.0019 μg/mL, respectively. Fang *et al.* [145] synthesized and evaluated the antibacterial activity of thiophene-pyrimidine hybrids against deadly antibiotic-resistant strains *i.e.* methicillin resistant *S. aureus* and vancomycin-resistant *Enterococcus*. Two hybrid derivatives **159** and **160** exhibited attractive antibacterial potential and inhibited the proliferation rate of *B. subtilis*, *S. aureus*, *E. faecalis* and *S. epidermidis* at a concentration (MIC) of 2 μg/mL.

**Anticancer activity:** Zhao *et al.* [186] reported the synthesis and anticancer activity of biaryl furo[2,3-*d*]pyrimidine derivatives as potent and selective *c*-Met kinase inhibitors. The most potent compound **161** displayed the $IC_{50}$ at 69.8 nM against *c*-Met kinase during *in vitro* enzymatic study. Kim *et al.* [187] synthesized and evaluated fused pyrimidine derivatives as potent Akt-1 kinase inhibitor. Compound **162** among the synthesized derivatives was reported with $IC_{50}$ value of 24 nM against Akt-1 kinase enzyme. Potent glycogen synthase kinase-3 (GSK-3) inhibitors with fused pyrimidine nucleus were synthesized by Miyazaki *et al.* [188]. Compound **163** with two-digit nanomolar activity ($IC_{50}$ = 32 nM) was further optimized to obtain more potent GSK-3β inhibitor **164** with $IC_{50}$ of 5 nM. A new series of aryl sulphonamide derivatives of pyrimidine were synthesized by Maeda *et al.* [189] and most active compound **165** exhibited the $IC_{50}$ value of 23 nM against GSK-3β enzyme during *in vitro* screening. Receptor-interacting protein 1 (RIP-1) inhibitors sharing pyrimidine pharmacophore in their structure were reported by Harris *et al.* [190]. Most potent compound **166** inhibited activity of RIP-1 kinase enzyme with $IC_{50}$ of 10 nM. Pyrimidine based aurora kinase A inhibitors were documented by Coumar *et al.* [191]. During structure optimization, compound **167** displayed $IC_{50}$ value of 24 nM against aurora kinase-A enzyme. Fused-pyrimidine derivatives as dual vascular endothelial growth factor (VEGF) receptor and Tie-2 receptor inhibitors were reported by Miyazaki *et al.* [192,193] as anticancer agents. The most potent compound **168** of the series exhibited $IC_{50}$ of < 3 nM against both the enzymes (VGEFR and Tie-2 receptor). Dual inhibitors of epidermal growth factor receptor (EGFR) and VEGFR were reported by Martin-Kohler *et al.* [194]. Several compounds with pyrimidine nucleus were synthesized but compound **169** demonstrated optimal VEGFR and EGFR inhibition potential with $IC_{50}$ value of 40 nM and 20 nM, respectively. Several multi-targeting kinase inhibitors were designed by Gangjee *et al.* [195]. Among synthesized compounds, two molecules **170** and **171** demonstrated potent multikinase inhibition potential. These compounds also limit the activity of dihydrofolate reductase enzyme. Liu *et al.* [196] had developed orally active pyrimidine-thiourea hybrids as antitumor agents. Compound **172** was found to be potent and selective histone lysine specific demethylase 1 (LSD1) inhibitor with half maximal inhibitory concentration ($IC_{50}$) of 0.65 μM against LSD1 enzyme and expressed cytotoxicity against human gastric cancer cell line (MGC-803). Wang *et al.* [197] also reported a cyano-pyrimidine derivative, GS 9901 (**173**), a potent anticancer candidate. This compound has undergone Phase 1 clinical trial for the treatment of various lymphomas and leukaemia.

Mohamed *et al.* [198] synthesized a series of 6-aryl-5-cyano thiouracil derivatives as anticancer agents. The C-2 and *N*-3 substituted analogues **174**, **175** and **176** displayed superior antiproliferative activity against hepatocellular carcinoma (HePG2), mammary gland breast cancer (MCF-7) cell lines than 5-fluororacil ($IC_{50}$ = 38.44 μM against HePG2 and 41.53 μM for MCF-7) with $IC_{50}$ value of 24.16 μM, 25.52 μM, 25.73 μM and 27.24 μM, 23.91 μM, 27.71 μM respectively. Furthermore, Shao *et al.* [199] synthesized substituted highly selective 4-thiazol-2-anilinopyrimidine derivatives, cyclin dependent kinase 9 inhibitor (CDK9), as anticancer agents. The most selective compound **177** bearing bulkier 1,4-diazepan-1-yl substituted aniline group at C-2 aniline was > 80-folds more selective towards CDK9 over CDK2 with $IC_{50}$ value of 7 nM. Compound **177** suppressed tumor cell proliferation with half maximal growth inhibitory concentration ($GI_{50}$) values ranging from 0.38 to 0.78 μM, irrespective of the tumor cell type. Pyrimidine analogue with substituted thaizole group at C-4 position and different bulkier substitutions on C-2 amino group gave potent and highly selective CDK9 inhibitor **178** with good antiproliferative activity ($GI_{50}$ =0.79 μM, 0.64 μM against HCT-116 and MCF-7 respectively) [200].

Senthilkumar *et al.* [201] had synthesized C-4 amine substituted cyanopyrimidine analogues and concluded that the cyano group at C-5 and NH- group at C-4 position of pyrimidine core is necessary to increase anticancer potency. Compound **179** exhibited stronger cytotoxic activity against Ehrlich ascites tumour (EAT) cells with an $IC_{50}$ value of 5.2 μM, comparable to the standard drug methotrexate (MTX) having an $IC_{50}$ value of 3.6 μM. Perreault *et al.* [202] had designed and synthesized 2-aminopyrimidine derivatives as phosphoinositide 3-Kinase (PI3K) β/δ inhibitor for treating Phosphatase and Tensin Homolog (PTEN) deficient tumors. The most active compound **180** bearing (3,4-dihydroquinazolin-2-yl)ethylamino side chain at C-4 position displayed good metabolic profile with $IC_{50}$ of 2.6 nM, 3.3 nM against PI3K β and PI3K δ, respectively. Introduction of amino functions, in the context of either *meta*- or *para*-substituted anilines at the C-2 pyrimidine ring, resulted in a significant increase of inhibitory activity not only against CDK2 but also against CDK9. Pyrimidine carbonitrile derivatives were synthesized and evaluated against NCI-60 cancer cell line panel to establish their anticancer activity by Cocco *et al.* [203]. Compound **181** exhibited $IC_{50}$ value of 2.95 μM and 2.49 μM against SF-268 and SNB-57 cell lines, respectively. Diversely substituted pyrimidine sulphonamide derivatives were synthesized and evaluated for their anticancer activities by El-Sayed *et al.* [204]. Compound **182** demonstrated superior anticancer activity with elongation in life span of mice than 5-fluorouracil. Fares *et al.* [205] reported pyrimidine based anticancer agent **183** that were effective against PC-3 and A549 cancer cells with $IC_{50}$ value of 0.36 μM and 0.41 μM, respectively. Hu *et al.* [206] synthesized anticancer agent **184** that inhibited the growth of A459 and SPC-A-1 cancer cell lines with $IC_{50}$ value of 0.8 μM. Huang *et al.* [207] had reported pyrazolopyrimidine anal-



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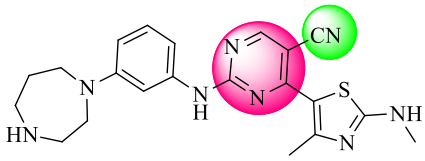

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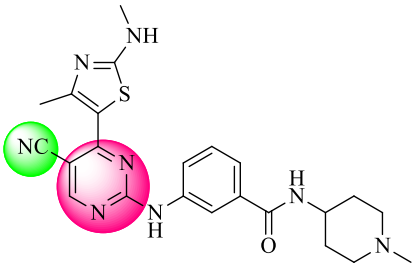

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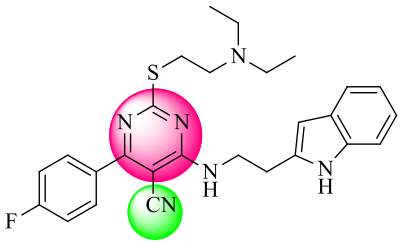

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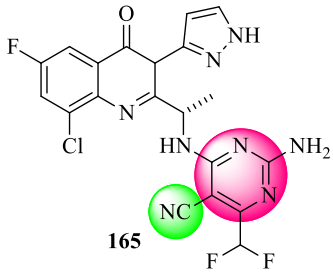

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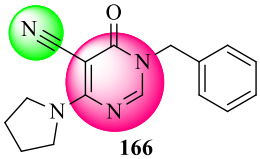

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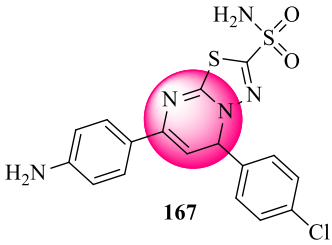

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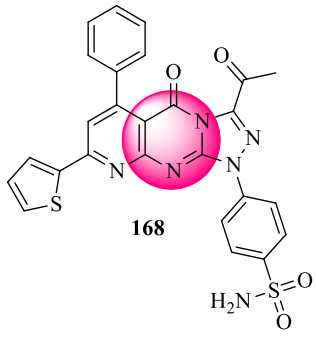

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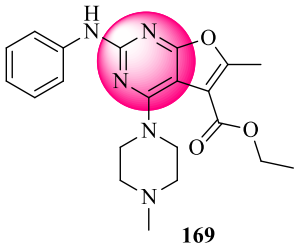

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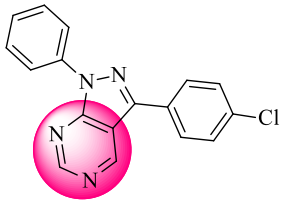

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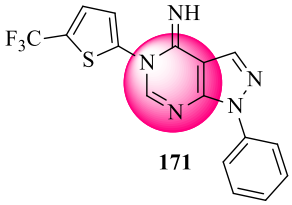

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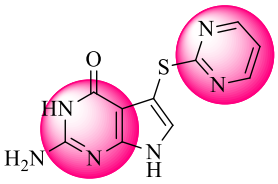

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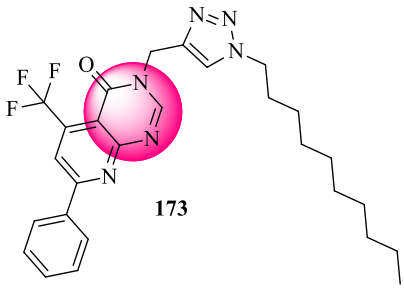

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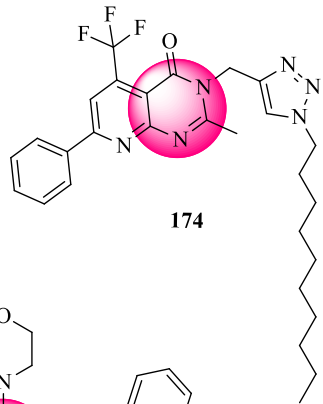

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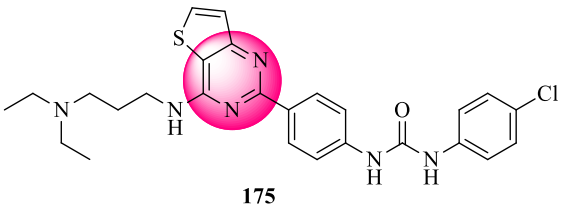

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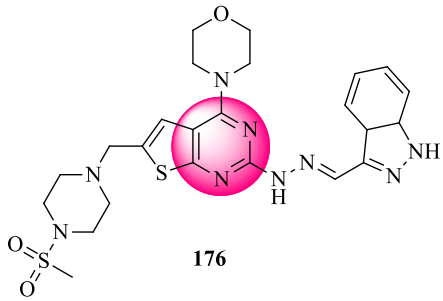

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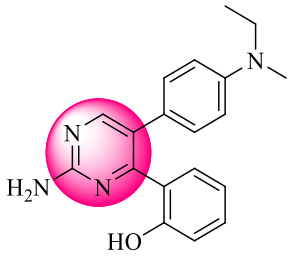

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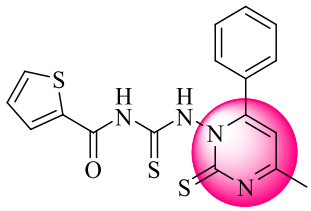

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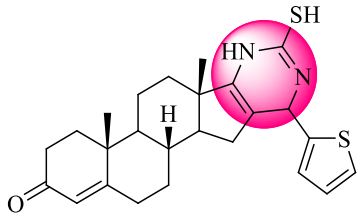

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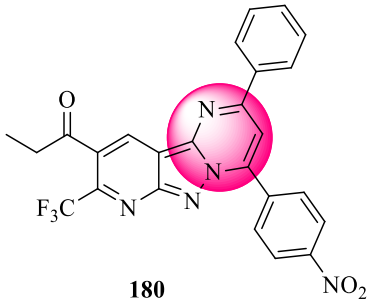

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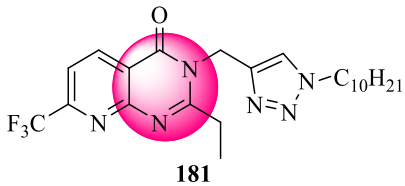

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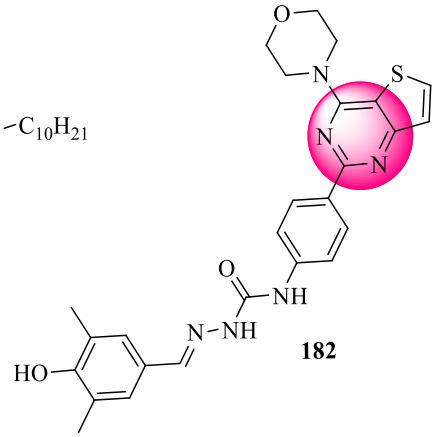

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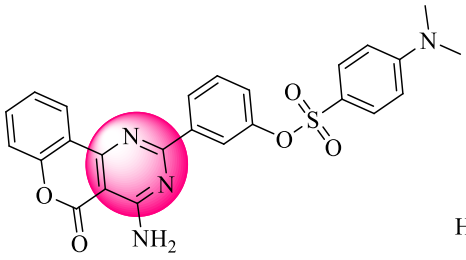

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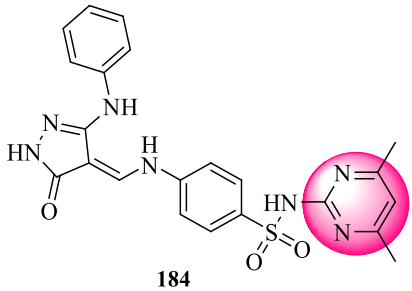

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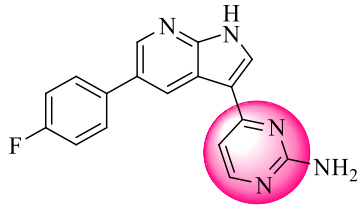

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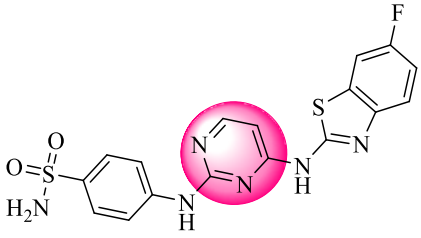

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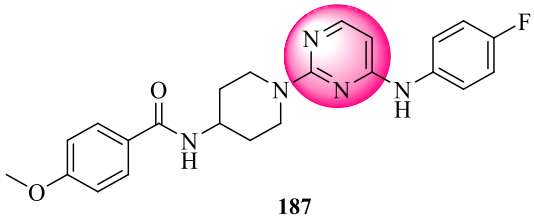

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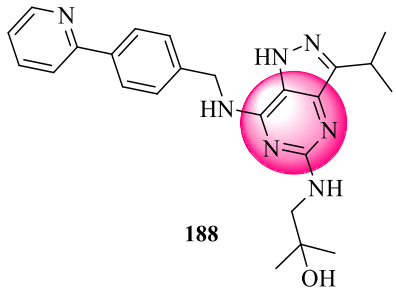

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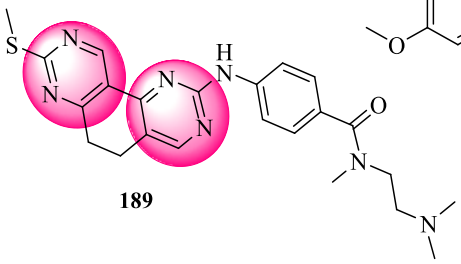

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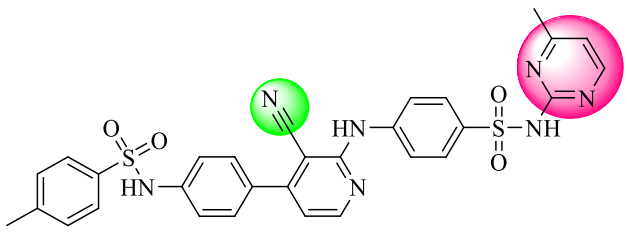

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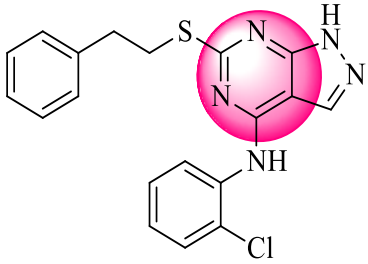

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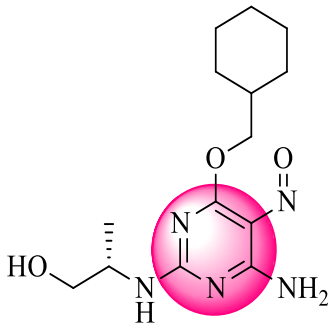

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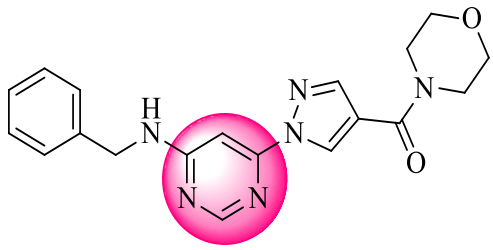

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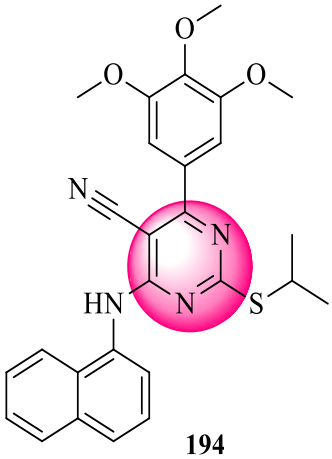

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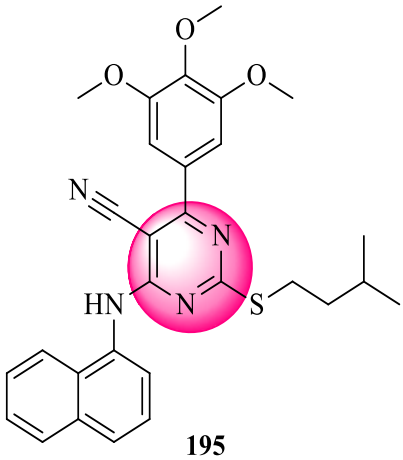

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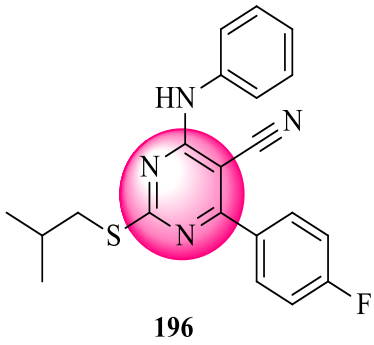

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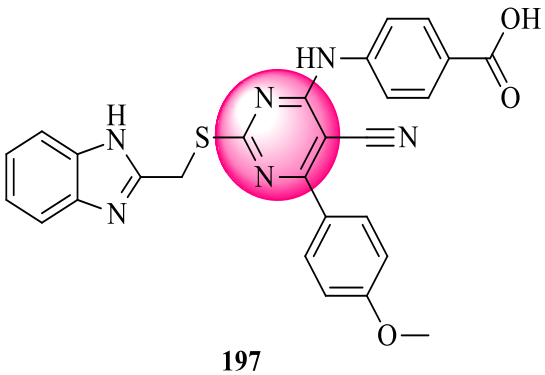

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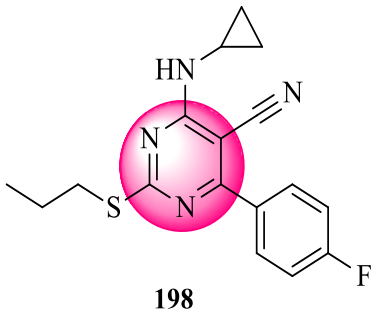

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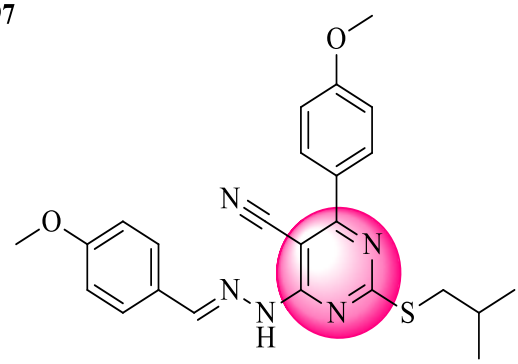


**199**

Structure of pyrimidine based anticancer agents

ogues as moderately active anticancer agents. The most active compound **185** exhibited $GI_{50}$ value of 18 μM and 23 μM against NCI-H226 and NPC-TW01 cell lines, respectively.

Song *et al.* [208] adopted green synthesis methodology to synthesize pyrimidine based potent anticancer agents. Compound **186** elicited more than two-folds potency against HL-60 cells than doxorubicin with $IC_{50}$ at 0.08 μg/mL and 0.21 μg/mL, respectively. Compound **187** inhibited growth of HCT116 cell line with $IC_{50}$ value of 17.61 μM [209]. Triazole-linked pyrimidine analogues as potent anticancer agents against leukemia and colon cancer cell lines were evaluated by Kurumurthy *et al.* [210]. Both the compound **188** and **189** exhibited superior anticancer activity than etoposide. Pyrimidine urea derivatives as potent anticancer agents were reported by Liu *et al.* [211]. The most active compound **190** elicited anticancer activity similar to sorafenib and exhibited strongest anticancer activity against H460 and HT-29 cancer cell lines with $IC_{50}$ value of 81 nM and 58 nM, respectively. Morpholine linked pyrimidine derivatives were designed and synthesized by Zhu *et al.* [212]. Most active compound **175** exhibited $IC_{50}$ at 0.84 μg/mL and 0.23 μg/mL against H460 and HT-29 cancer cell lines, respectively. Xie *et al.* [213] synthesized potent nanomolar active anticancer agent **176** that showed potent antiproliferative activity against a penal of five cancer cell lines ranges from 24 nM to 55 nM. Several fused pyrimidine derivatives were synthesized and evaluated for their anticancer activity against HEPG2 cancer cell line as reported by Al-Issa [214]. Most active compound **177** restricted the proliferation of HEPG2 cell line with $IC_{50}$ value of 17.4 μg/mL. Mohareb *et al.* [215] developed nanomolar active compound **178** against NUGC gastric cancer cell line with anticancer potential ($IC_{50}$) of 40 nM. Compound **180** synthesized by Kumar *et al.* [216] displayed potent anti-proliferative activity against MDA-MB-231 with inhibition potential ($IC_{50}$) of 10.3 μM. Kumar *et al.* [217] synthesized novel triazole/isoxazole functionalized 7-(trifluoromethyl)-pyrido[2,3-*d*]-pyrimidine derivatives and found that in this series, compound **181** displayed potent anticancer activity against PANC1 cancer cell line with $GI_{50}$ value of 20 nM found superior than nocodazole ($GI_{50}$ = 29 nM). Theinopyrimidine derivative **182** also expressed attractive nanomolar inhibitory profiler against H460 and HT-29 cancer cell lines with $IC_{50}$ value of 57 nM and 39 nM, respectively [218]. The anticancer activity of this derivative was found superior than the anticancer potency of sorafenib. Similarly, Lv *et al.* [219] had reported phenylpyrimidine based potent anticancer agents that had shown superior potency than sorafenib. The most potent compound **182** was found more potent that doxorubicin when tested against Cal27, CNE2, KB cancer cell lines with $IC_{50}$ value of 1.97 μM, 1.92 μM and 3.72 μM, respectively. Ali *et al.* [220] had reported pyrazolopyrimidine derivatives as potent cyclin-dependent kinase inhibitors. The most potent compound **183** exhibited superior *in vitro* CDK2 inhibition, whereas compound **184** displayed highest antiproliferative activity against MCF-7 cell line with $IC_{50}$ at 10.05 μM during *in vitro* cytotoxicity assay. Singh *et al.* [221] described the synthesis and potent CDK2 and CDK9 inhibitory potentials of pyrimidinylazaindoles. The most active compound **185** inhibited CDK2 and CDK9 activity with $IC_{50}$ values of 5.5 nM and 24 nM, respectively. Diao *et al.* [222] also developed novel several pyrimidine-linked benzothiazole hybrids and the most potent compound **186** from this series was found three times more potent than reference AZD5438 against CDK2 enzyme with inhibition potential of 15.4 nM. Wang *et al.* [223] synthesized pyrimidine derivative **187** and inhibited CDK2 enzyme ($IC_{50}$ = 45.8 nM) as well as exhibited $IC_{50}$ value of 5.74 μM against MDA MB-468 cancer cell line. Vymetalova *et al.* [224] had designed and synthesized potent dual CDK2 and CDK5 inhibitors as anticancer agents. Com-pound **188** found to be the most active compound of the series with $IC_{50}$ of 9 nM and 1 nM against CDK2 and CDK5 enzyme, respectively. Hu *et al.* [225] synthesized quinazoline-pyrimidine hybrids as potent CDK2 inhibitors and found that compound **189** exhibited best CDK2 inhibition profile with $IC_{50}$ value of 0.09 μM. Similarly, sulfonamide functionalized pyrimidine derivatives were synthesized as potent anticancer agents by Ghorab *et al.* [226], where compound **190** exhibited anticancer potency against MCF-7 cell line with $IC_{50}$ value of 18.3 μM.

Cherukupalli *et al.* [227] reported Abl kinase inhibitors with pyrimidine nucleus and found that the most active compound **191** with $IC_{50}$ value of 7.8 μM against CDK2 enzyme. Cortese *et al.* [228] synthesized $N^2$-substituted 2,4-diamino-6-cyclohexylmethoxy-5-nitrosopyrimidines and related 5-cyano-NNO-azoxy derivatives as cyclin-dependent kinase 2 (CDK2) inhibitors. Among the synthesized compounds, compound **192** displayed CDK2 inhibitory profile with $IC_{50}$ value of 0.16 μM. Vekariya *et al.* [229] also documented the synthesis of pyrimidine-pyrazole hybrid as CDK2 inhibitor. These compounds exhibited CDK2 inhibitory potency ($IC_{50}$) less than 20 nM and also found that compound **193** was reported as prototype compound. Nainwal *et al.* [230] also synthesized and evaluated the anticancer potential of 3,4,5-trimethoxy phenyl fragment bearing cyanopyrimidine analogues against NCI-60 cancer cell lines. The most active compound **194** bearing α-naphthylamine ring containing derivative displayed strong apoptotic and broad-spectrum anticancer activity with %growth inhibition of 85.28%, 75.22%, 72.46% against SR (leukemia), HCT-116 (colon) and NCI-H460 (small-lung) cancer cell lines, respectively. Among the isopropyl and isobutyl side chain derivatives, isopropyl cyanopyrimidine derivatives exhibited superior antiproliferative potential than isobutyl derivatives. In continuation of their previous work, Nainwal *et al.* [231] further modified the cyanopyrimidine pharmacophore and developed 2,4,6-trisubstituted isopentyl analogues of pyrimidine-5-carbonitrile as promising apoptotic agents. In this series, α-naphthylamine fragment containing analogue **195** exhibited superior broad anticancer profile and inhibited the growth of HCT-116 colon cancer, SR leukemia cancer cell lines by 76.94% and 84.01%, respectively.

Akhter *et al.* [232] synthesized and evaluated the *in vitro* anticancer and *in vivo* anti-inflammatory activity of 6-(4-fluorophenyl) cyanopyrimidine derivatives. The most active compound **196** of this series displayed quite attractive and superior anticancer activity against ovarian cancer than 5-fluorouracil with $GI_{50}$ value of 0.33 μM and 4.43 μM, respectively. The selectivity index of was found to be 4.84 and quite

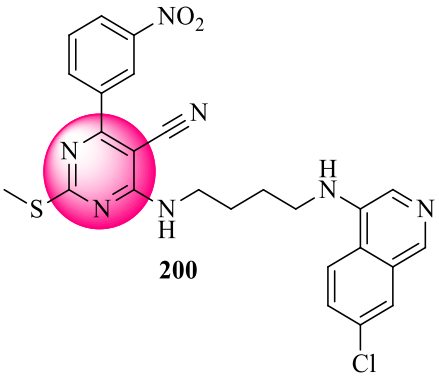
equivalent to 5-fluorouracil. It also displayed an attractive *in vivo* anti-inflammatory activity in rat paw oedema model with 87% reduction in inflammation after 3 h of administration which was reported superior than selective COX-2 inhibitor celecoxib (82%) and non-selective anti-inflammatory drug ibuprofen (78%). Compound **196** was highly selective for COX-2 enzyme over COX-1 with $IC_{50}$ value of 0.91 μM and 95.29 μM, respectively. Morpholine based pyrimidine-benzimidazole hybrids were synthesized by Wang *et al.* [233] as anbtiproliferative agents. The most active compound **197** inhibited the growth of T-47D (breast cancer), HOP-92 (non-small lung cancer) cell lines by 84.19% and 88.44% respectively at 10 μM. Replacement of morpholine ring with any other heterocyclic ring decreased the anticancer potential of the benzimidazole-pyrimidine hybrids. Sheikh *et al.* [234] had reported LSD-1inhibitor based on cycloproyl-linked pyrimidine carbonitrile derivatives as anticancer agents and compound **198** displayed $IC_{50}$ value 1.80 μM. Tasneem *et al.* [235], reported hydrazone-pyrimidine carbonitrile analogue **199** as LSD-1 inhibitor with $IC_{50}$ value of 0.956 μM. Compound **199** exhibited highest anticancer activity against OVCAR-4 breast cancer and HOP-62 non-small lung cancer cells with $GI_{50}$ value of 0.417 μM and 0.414 μM.

**Antimalarial activity:** Kaur *et al.* [236] designed and synthesized pyrimidine-linked primaquine hybrids as antimalarial agents. Among these derivatives compound **200** had shown most potent antiplasmodial activity with $IC_{50}$ value of 56 nM against the blood and liver stage Dd2 *Plasmodium falciparum.* Kalaria *et al.* [237] carried out one pot synthesis of several heterocyclic fused pyran derivatives. Among the synthesized derivatives, pyrimidine ring containing molecule **201** expressed superior antimalarial activity against *P. falciparum* with $IC_{50}$ value of 0.049 μg/mL. Gonzàlez *et al.* [238] documented the synthesis, antimalarial activity and SAR of diaminopyrimidine analogues. The most active compound **202** displayed brilliant antimalarial activity during *in vivo* studies in mice against *P. falciparum* at a dose of 50 mg/kg. Mendoza-Martínez *et al.* [239] had reported quinazoline-pyrimidine hybrids as antimalarial agents and the most active compound **203** displayed 100% suppression in parasitemia. Pyrimidine based antimalarial candidate **204** reported by Dahlgren *et al.* [240] inhibited K1 strain of *P. falciparum* with $IC_{50}$ value of 1.6 μM. An efficient one pot synthesis of thiazolopyrimidine derivatives were carried out by Fatima *et al.* [241]. The most active compound **205** inhibited *P. falciparum* K1 and 3D7 strains with $IC_{50}$ value of 0.27 μg/mL and 0.5 μg/mL, respectively. Cui *et al.* [242] synthesized pyrimidine derivative **206** that exhibited superior antiplasmodial activity among the synthesized analogues. It inhibited *P. falciparum* aeAZT strain with $IC_{50}$ value of 67 μM. Mane *et al.* [243] documented pyrimidine based antimalarial agents asfalcipain-2 inhibitor. The compound **207** and **208** inhibited *Plasmodium* falcipain-2 enzyme with $IC_{50}$ value of 6 μM and 7 μM, respectively. Sharma *et al.* [244] synthesized and evaluated antimalarial potency of quinolinyl pyrimidines analogues against NF-54 strain of *P. falciparum.* The most active compound **209** displayed $IC_{50}$ value of 1 mg/mL. Aminake *et al.* [245] had synthesized pyrimidine fused atemisinin hybrid compounds as antimalarial agents. The most potent derivative **210** displayed antimalarial activity comparable to artemisinin against 3D7 and Dd2 strains with $IC_{50}$ value of 0.03 μM and 0.01 μM, respectively.

Hampton *et al.* [246] reported nucleoside derivatives for targeting *P. falciparum* deoxyuridine nucleotidohydrolase (dUTPase) enzyme. The most active compound **211** exhibited $IC_{50}$ and $EC_{50}$ value of 0.2 μM and 7.2 μM during *in vitro* enzymatic and cell-based assay. Diversely substituted pyrimidine analogues were reported for their antimalarial potentials by Azeredo *et al.* [247]. The most active compound **212** inhibited the activity of *P. falciparum* dihydroorotate dehydrogenase (*Pf*DHODH) with $IC_{50}$ value of 0.023 μM. Insuasty *et al.* [248] designed pyrimidine-diazepines derivative **213** as antimalarial agent and inhibited *P. falciparum* 3D7 strain with $IC_{50}$ value of 11.3 μg/mL. Satasia *et al.* [249] reported the synthesis and antimalarial activity of pyridopyrimidine based compounds against *P. falciparum*. Two most active compounds **214** and **215** reported to have $IC_{50}$ value of 0.033 μg/mL. Kumar *et al.* [250] carried out synthesis of 4-aminoquinoline-pyrimidine hybrids as antimalarial agents against *P. falciparum* D6 and W2 strains. The most potent compound **216** was documented with $IC_{50}$ value of 0.019 μM against CQ-sensitive strains. Maurya *et al.* [251] had reported potent antimalarial agent **217** as *Pf*DHFR inhibitor. Agarwal *et al.* [252] developed 2,4,6-trisubstituted pyrimidine compound **218** as *in vitro* antimalarial agent with antimalarial activity equivalent to pyrimethamine against *P. falciparum*. Pretorius *et al.* [253] synthesized pyrimidine-based derivatives that were active against *P. falciparum* D10 and Dd2 strains. Most potent derivative **219** was reported with $IC_{50}$ value of 0.157 μM against both the strains. Azeredo *et al.* [247] reported compound **220** as *Pf*DHODH inhibitor with good *in vivo* efficacy against *P. berghei* in mice model. Pyrimidine sulfonamide derivatives synthesized as antimalarial agent against *P. falciparum* D6 and W2 strains by Yadav *et al.* [254] and found that compound **221** was reported with high antimalarial activity comparable to artemisinin.

## Conclusion

Based on the collective findings, the pyrimidine scaffold is a highly effective structural platform for the development of biologically active small molecules. More than 147 pyrimidine-based and pyrimidine-fused molecules are approved by the USFDA for the clinical treatment of various diseases. About 36% of the FDA approved pyrimidine derivatives are anticancer agents, 19% are antiviral drugs and 14% of the drugs are used in the management and treatment of cardiovascular disorders. Modifications at key positions of the ring, incorporation of electron-withdrawing substituents, fusion with additional heterocycles and linkage to pharmacophoric moieties consistently produced derivatives with enhanced potency across multiple therapeutic categories including anti-inflammatory, antileishmanial, antidiabetic, anti-Alzheimer's, antihypertensive, anticonvulsant, antimicrobial and anticancer activities. Analysis of structure–activity relationships indicates that substitution patterns strongly influence molecular recognition, target affinity and physico-chemical properties. The



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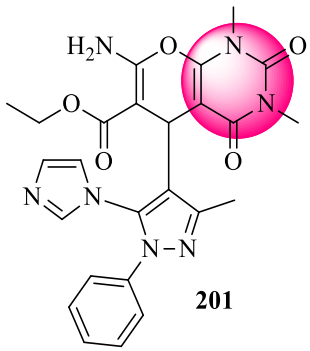

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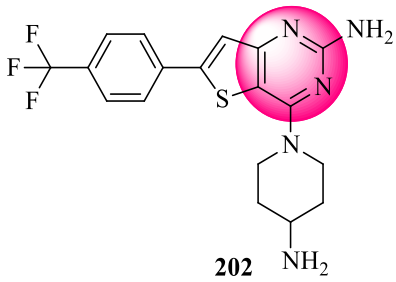

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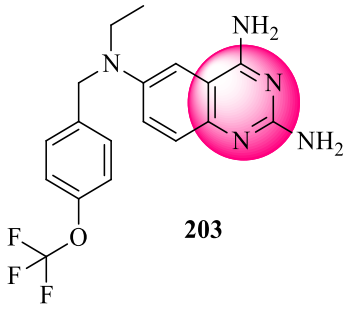

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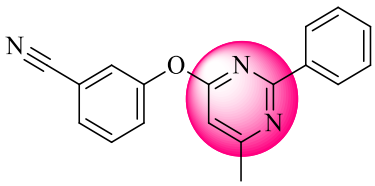

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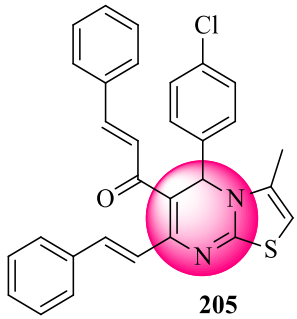

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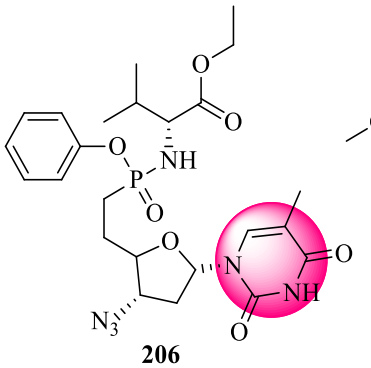

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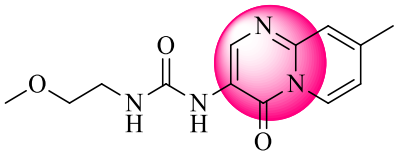

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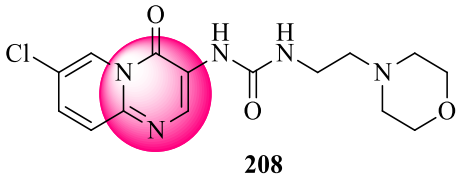

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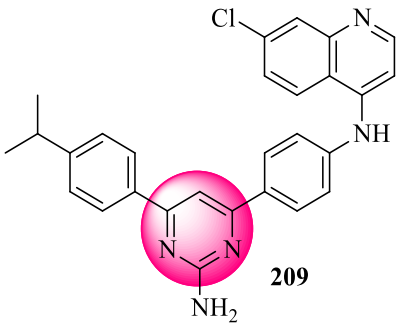

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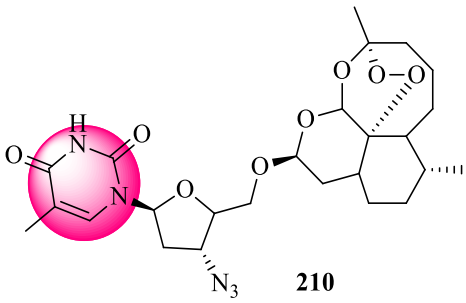

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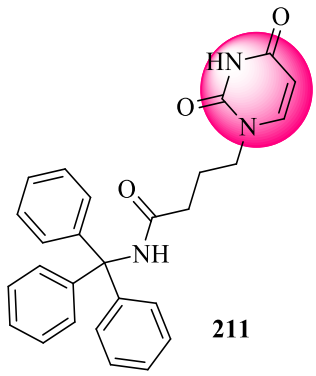

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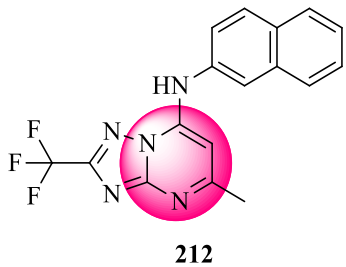

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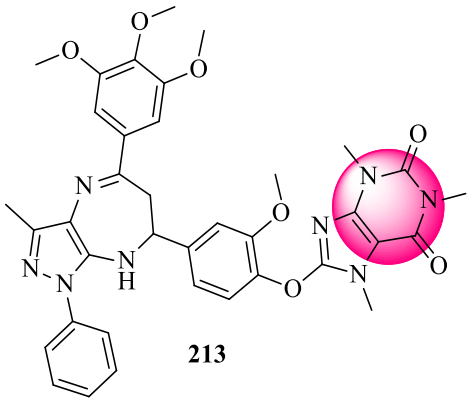

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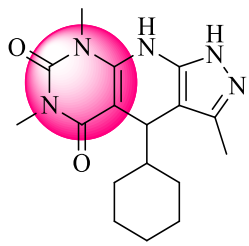
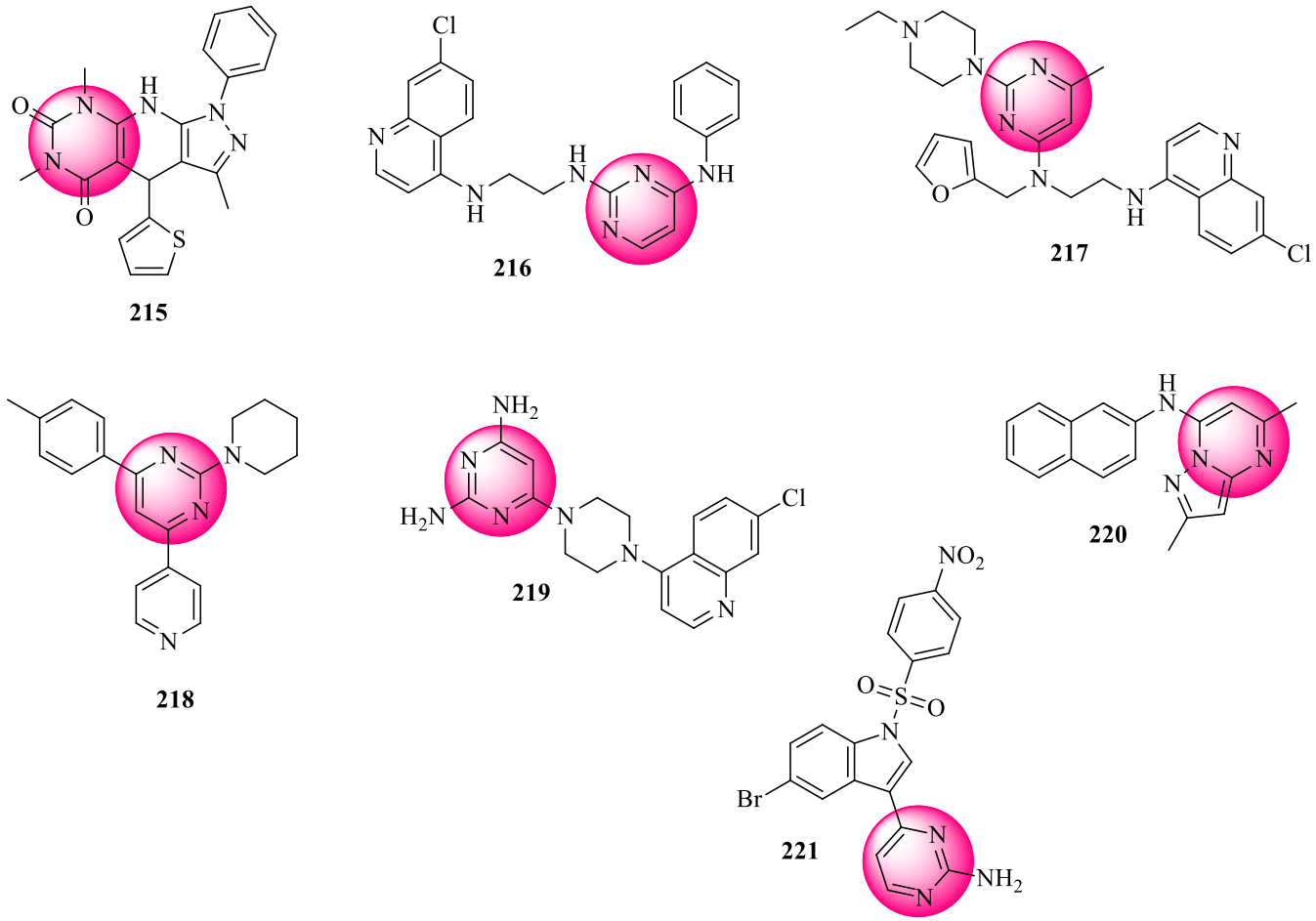


214




Structure of pyrimidine based antimalarial agents

heteroatom-rich linkers, thiosemicarbazide and thiadiazole fragments, hydrazone systems and coumarin-based hybrids frequently contributed to improve the bioactivities. Several derivatives demonstrated activity comparable to or exceeding standard drugs, indicating their potential as lead compounds. Despite these advances, most reported molecules remain in the preliminary discovery phase. Data on pharmacokinetics, metabolic stability, selectivity and toxicity are limited and require systematic evaluation. Further optimization through computational modelling, mechanistic studies and extended biological assays is essential to determine the translational potential of these scaffolds. Overall, pyrimidine-based derivatives remain a robust and versatile foundation for future drug development. Continued structural refinement and comprehensive biological assessment are expected to support their progression toward clinically relevant therapeutic candidates. This review will be helpful for researchers and scientists in designing and developing pyrimidine-based potent, efficacious and less toxic newer therapeutic agents.

## ACKNOWLEDGEMENTS

One of the authors, Lalit Mohan Nainwal gratefully acknowledges Council of Scientific & Industrial Research (CSIR), Government of India, for the financial support by the CSIR SRF grant (*via* letter No. 09/591(0151)/2018-EMR-I).

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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