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Review

Current Study on Biological and Synthetic Applications of Aryl Pyrimidines

Boja Poojary*, Preethi

Department of Chemistry, Mangalore University, Mangalagangohri-574199, Karnataka, India

ABSTRACT

Pyrimidine is a heteroaromatic compound containing two nitrogen atoms at positions 1 and 3 of the six-membered ring which shows a wide range of biological properties. Pyrimidines occupy a central position due to their presence in the genetic material of cells. Pyrimidine derivatives have been shown to have anticonvulsant, analgesic, sedative, anti-depressive, antipyretic, anti-inflammatory, antiviral, anti-HIV, antimicrobial and anti-tumor properties. This review gives the way forward for research work reported in the recent scientific literature on various biological activities of pyrimidine analogues.

Keywords: Pyrimidine; Biological activity; Anti-cancer; Anti-microbial; Anti-convulsant; Anti-diabetic

INTRODUCTION

The chemistry of heterocyclic compounds is important for the discovery of novel drugs. Pyrimidine pharmacophores are an important and integral part of DNA and RNA and they play an important role in several biological processes. They also have significant chemical and pharmacological utility as antibiotics, antibacterial, cardiovascular, agrochemical and veterinary products. These derivatives were discovered to have a variety of activities, including Anti-inflammatory, analgesic properties, antimicrobial properties, anti-avian influenza virus (H5N1), anti-herpes Simplex Virus type-1 (HSV-1) and Hepatitis-A virus (HAV), serotonin 5-HT6 receptor antagonist, anti-arrhythmic agents and so on [1].

Pyrimidines have a unique place in organic and medicinal chemistry due to their high biological activity. The pyrimidine core is a structural component of vital biomolecules such as DNA as well as critical drugs such as Fluorouracil, Etravirine, Risperidone, Iclaprim, Avanafil and Rosuvastatin [2].

Biological aspects

Pyrimidines are a broad class of compounds that have received a lot of attention because of their diverse biological activities such as anti-inflammatory, COX inhibition, anti-cancer, anti-allergic, analgesic and so on [3]. A brief description of the various biological activities of pyrimidine derivatives is substantiated below.

Pyrimidines as anti-Alzheimer's agents

Alzheimer's Disease (AD) is a neurodegenerative disorder that causes dementia in more than half of all cases. Over the last decade, significant efforts have been made to determine the etiopathogenesis of the disease, as well as to perform early diagnosis and therapeutic control of the disorder. There is currently no drug on the market that provides a specific solution for treating Alzheimer's disease. The pharmacological treatment consists of two types of drugs: Acetylcholinesterase Inhibitors (AchEI) and glutamate modulators [4].

Synthesized two series of novel N-aryl-7-methoxybenzo[b]furo[3,2-d] pyrimidine-4-amines and their N-aryl-7-methoxybenzo[b]thieno[3,2-d]pyrimidine-4-amine analogues using microwave radiation *via* a Dimroth rearrangement. The synthesized compounds were CDK5/p25 (cyclin-dependent kinase), CK1/(casein kinase 1), GSK3/ (glycogen synthase kinase 3), DYRK1A (dual-specificity tyrosine phosphorylation regulated kinase) and CLK1 were tested *in-vitro* to evaluate their inhibition potential on five different kinases (cdc2-like kinase 1). Among these compounds, the benzothieno [3,2-d] pyrimidine derivatives 1 and 2 showed sub-micromolar inhibition and selectivity for CLK1 and DYRK1A kinase [5].

Designed, synthesized and characterized a series of N-aryl benzo [b] thieno [3,2-d] pyrimidin-4-amines and their pyrido and pyrazine analogues *via* microwave-accelerated condensation using Dimroth rearrangement. The final products were tested for

Correspondence to: Boja Poojary, Department of Chemistry, Mangalore University, Mangalagangohri-574199, Karnataka, India, Tel: +919448865403; E-mail: bojapoojary@gmail.com

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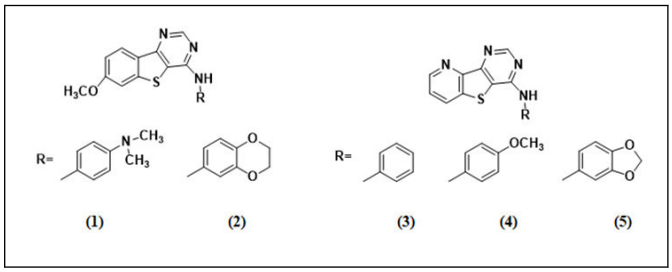
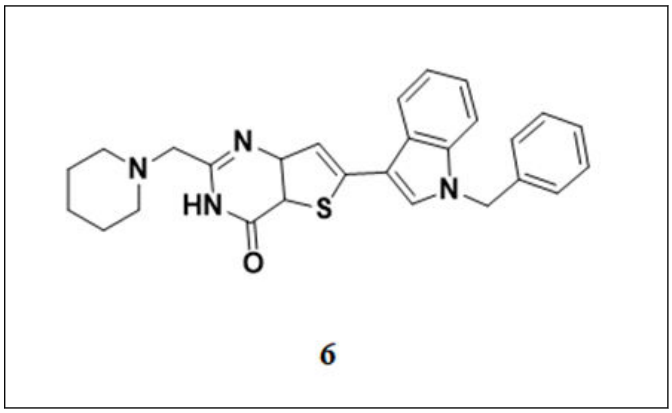
inhibitory potency against five Ser/Thr kinases (CDK5/p25, CK1/, CK1/, DYRK1A, and CLK1). The N-aryl pyrido [3',2': 4,5] thieno [3,2-d] pyrimidin-4-amine derivatives 3, 4 and 5 were discovered to be potent CK1 and CLK1 kinase inhibitors [6].



Pyrimidines as anti-angiogenic agents

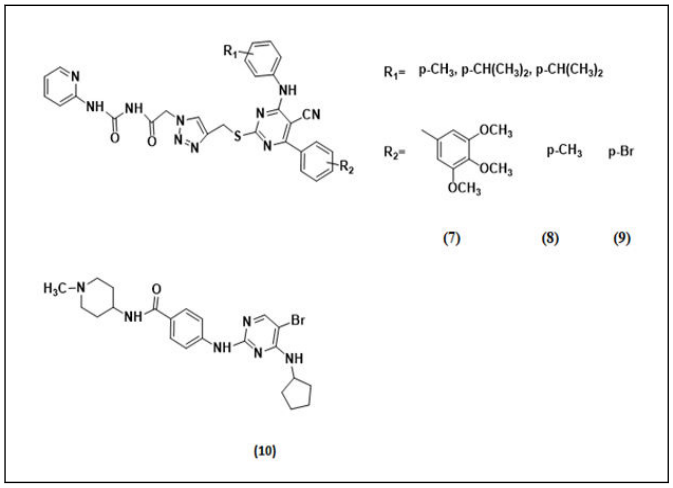
Angiogenesis is the process of creating new capillaries from existing vasculature to form new blood vessels, and it is a normal process for organ development. When controlling mechanisms of angiogenesis fail, it may play a role in the development and progression of diseases such as rheumatoid arthritis, inflammation, ocular neovascularization, psoriasis, tumor growth and metastasis. This process involves over twenty different factors, one of which is vascular endothelial growth factors (VEGFs). The VEGF family consists of VEGF-A (commonly referred to as VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and a structurally related molecule, Placental Growth Factor [7].



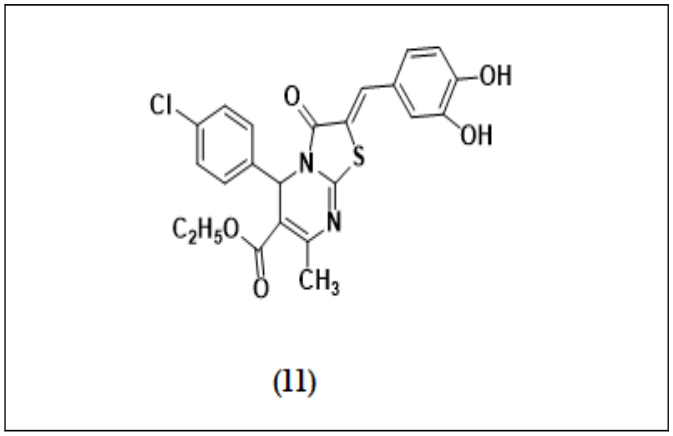
Pyrimidines as anti-cancer agents

Cancer is a life-threatening disease that affects more than six million people worldwide each year. Human's lifestyles have changed dramatically, increasing their risk of developing various types of cancer. There has been an ongoing effort to identify molecules with anti-cancer properties from both natural and synthetic sources [8]. There are various types of receptors involved in cancer progression, such as p21 activated kinases (PAKs), MCF-7 kinase, PKCK2 kinase, JAK1-3kinase, FLT1 kinase, FLT3-4 kinase, CHK1 kinase, Aurora-A kinase, MGC-803 kinase, EC-109 kinase and B16-F10 kinase etc.

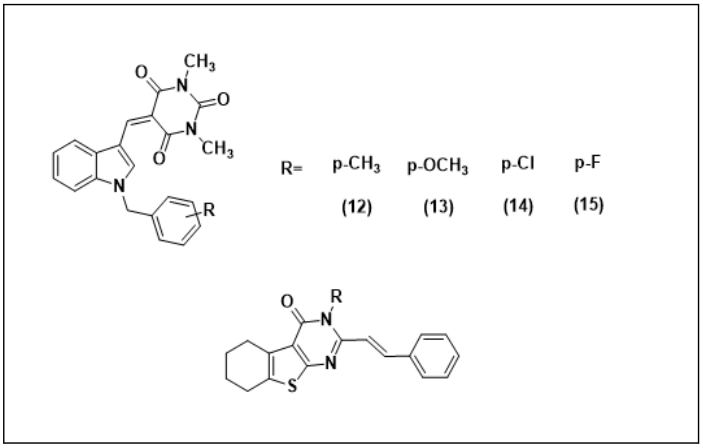
Designed, synthesized and tested 1,2,3-triazole–pyrimidine–urea derivatives for anticancer activity. These compounds were tested against four different cell lines: MGC-803, EC-109, MCF-7 and B16-F10. Almost all of the compounds synthesized demonstrated moderate to potent activity against all cancer cell lines. Compounds 7,8,9 and 10 on the other hand, demonstrated promising growth inhibition against B16-F10 (IC50=32 nM, 35 nM, and 42 nM respectively). A flow cytometry study also revealed that compound 7 induced cellular apoptosis in a concentration-dependent manner [9].



Created, synthesized and characterized ethyl 2-(benzylidene)-7-methyl-3-oxo-2,3-dihydro-5H-thiazolo[3,2-a] pyrimidine-6-carboxylates. Compound 11 was discovered to be a good PKCK2 inhibitor with an IC50 of 0.56 M, which is 2.2-fold more potent and selective than 4,5,6,7-tetrabromobenzotriazole (TBB) with an IC50 of 1.24 M. Compound 11 and TBB had Ki values of 0.78 M and 2.70 M for PKCK2, respectively. As a result, compound 11 inhibited endogenous PKCK2 kinase and demonstrated promising antiproliferative activity that warrants further investigation [10].

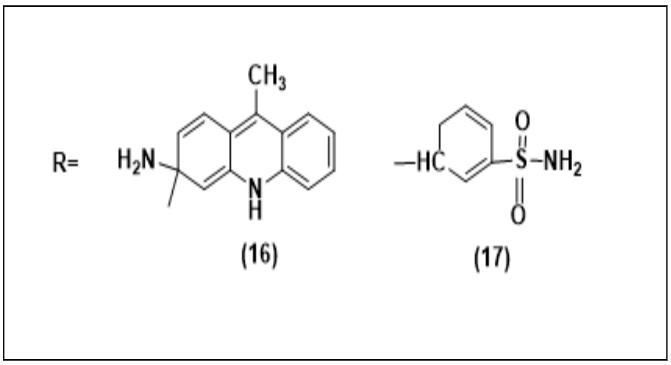


Produced a library of substituted 5-((1-benzyl-1H-indol-3-yl) methylene)-1,3-dimethyl pyrimidine-2,4,6(1H,3H,5H)-triones. All of the synthesized compounds were tested for *in-vitro* cell growth inhibition and cytotoxicity on 60 different types of human tumor cell lines. Compounds 12, 13, 14 and 15 were discovered to be extremely effective anti-cancer agents against ovarian, renal and breast cancer cell lines.

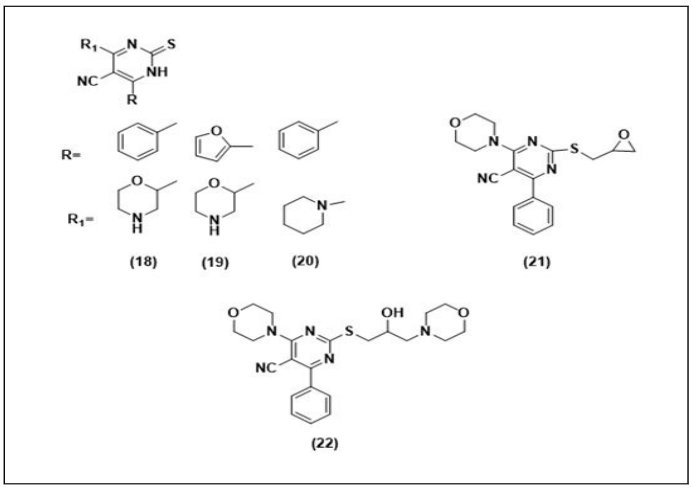


4-Methoxy-N-benzyl analogue (13) was the most active compound against OVCAR-5 ovarian cancer cells and MDA-MB-468 breast cancer cells, with GI50 values of 20 nM and 40 nM, respectively. Compounds 12 and 15 were found to be equally effective against MDA-MB-468 cells (GI50=30 nM). Compound 14 was found to be the most effective against the A498 renal cancer cell line (GI50=40 nM). These compounds, according to the findings, could serve as a starting point for the development of candidate drugs to treat a variety of solid tumors [11].

Designed, synthesized, characterized and tested for antitumor activity two series of new tetrahydro benzo[4,5]thieno[2,3-d]pyrimidines, 2,3-disubstituted derivatives and 2,4-disubstituted derivatives. When compared to standard Doxorubicin (IC50=5.46 mM), compound 16 demonstrated superior antitumor activity against breast MCF-7 (IC50=0.19 mM). In comparison to Doxorubicin (IC50=7.36 mM), compound 17 was the most active against the liver HEPG-2 cancer cell line (IC50=1.29 mM) [12].

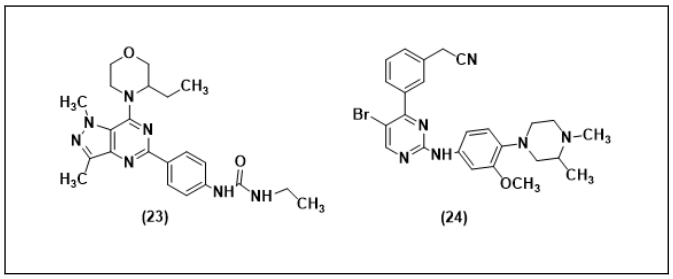


Designed synthesized and characterized pyrimidine-5-carbonitrile analogues. Selected members of the synthesized compounds were tested for anticancer activity against human tumor cell lines. The anticancer compounds found to be the most active were 18, 19, 20, 21 and 22. Compounds 21 and 22 were found to have strong interactions with the dihydrofolate reductase enzyme [13].



N-7-Methyl-imidazolopyrimidine derivatives were designed, synthesized and characterized by Lee et al. The anticancer potential of all the synthesized compounds was evaluated based on the hypothesis that the N-7-methyl substituent on imidazole pyrimidines would show selectivity for mTOR over the related PI3K and kinases. The most potent compound was discovered to be the pyrazolo [4,3-d]pyrimidine derivative 23 [14].

Synthesized and tested a new series of 2-arylamino-4-aryl-pyrimidine derivatives in various colon cancer cell lines for PAK1 kinase inhibitor anticancer properties. Compound 24 was discovered to be a potent PAK1 kinase inhibitor. Compound 24's kinase selectivity was investigated by screening against 81 of 118 different kinases. Compound 24 inhibited the kinases JAK1-3, FLT1, FLT3-4, CHK1, and Aurora A strongly, indicating a broad selective profile. Gini coefficient = 0.40 was used to determine the overall selectivity of this molecule [15].



Pyrimidines as anti-convulsant agents

Epilepsy is a neurological disorder characterized by an enduring proclivity to generate seizures as a result of abnormal neuronal activity in the brain. Epilepsy is the third most deadly neurological disorder, according to epidemiological studies, and it affects more than 50 million people worldwide, with the majority of these patients living in developing countries. Antiepileptic Drugs (AEDs) are a diverse group of molecules that work primarily by increasing inhibitory-Aminobutyric Acid (GABA) neurotransmission, modulating voltage-gated ion channels (Na+,Ca++) decreasing excitatory and primarily glutamate-mediated neurotransmission [16].

Designed, synthesized and characterized new substituted pyrimidine derivatives. All of the synthesized compounds were tested for anticonvulsant activity. Compound 21 was found to be the most potent of all and performed even better than standard Carbamazepine, with a relative potency of 2.53. The ED50 was calculated and was found to be 11 mg/kg. As a result, this can be used as a starting point in the search for a safer and more effective anticonvulsant agent [16]. Created, synthesized and characterized a series of 5-alkoxytetrazolo [1,5-c] thieno[2,3-e] pyrimidine derivatives and assessed their anticonvulsant activity [17].

Pyrimidines as anti-diabetic agents

Diabetes mellitus is a metabolic disorder caused by impaired insulin secretion from pancreatic -cells that is one of the three leading causes of death worldwide. Hyperglycemia is linked to changes in lipid parameters, which can lead to cardiovascular complications [1]. GPR119 is a G-protein coupled receptor that primarily acts on pancreatic beta cells and enteroendocrine cells in the intestine.

These GPR119 agonists, which include oleoyl ethanolamine (OEA), lysophosphatidylcholine, N-oleoyl dopamine and olivanic, have been shown to stimulate glucose-dependent insulin secretion *in vitro* and lower high blood glucose levels *in vivo* [18].

Inhibitors of sodium-glucose cotransporters (SGLTs) are a novel approach to diabetes treatment because their action of lowering blood glucose is insulin-independent. SGLT2 inhibitors may cause significant calorie loss by increasing glucose excretion into urine [19].

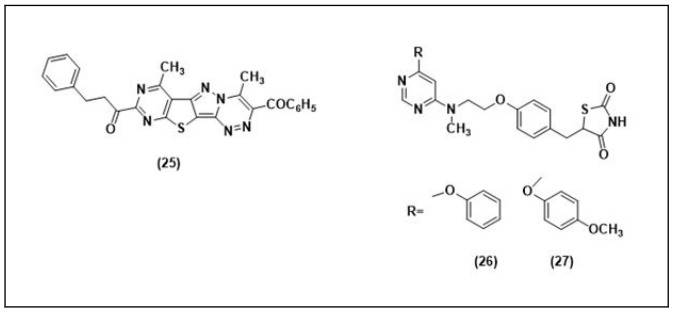
As a result, the ever-increasing disease burden caused by type 2 diabetes mellitus (T2DM) has encouraged the ongoing search for new therapies.

Al-Harbi et al. created and synthesized a novel class of poly-fused pyrazolothieno pyrimidine derivatives. All of the compounds synthesized were tested for hypoglycemic activity against standard pioglitazone (i. p., 5 mg/kg).

The standard and all of the synthesized compounds were found to have equipotent hypoglycemic activity (37.22.1-121.55.7). Compound 25 has been identified as a potential hypoglycemic agent [1].

Designed, synthesized and tested C-glucosides with a heteroaromatic ring for their inhibitory activities against SGLT2 in high-fat diet-fed KK (HF-KK) mice [19].

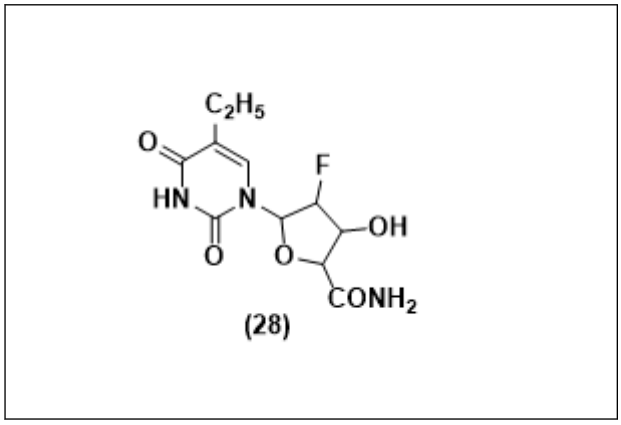
Designed and synthesized novel thiazolidinedione-modified pyrimidine's. These synthesized compounds were tested for their ability to lower blood glucose levels. Compounds 26 and 27 were found to be significantly more potent than the reference compounds, pioglitazone and rosiglitazone, in terms of antidiabetic activity [20].



Pyrimidines as anti-hepatitis agents

Hepatitis B and C viruses (HBV and HCV) are the leading causes of chronic liver disease in humans. Co-infection with both HBV and HCV is common and is linked to an increased risk of liver disease, cirrhosis and hepatocellular carcinoma, all of which are fatal. Due to the limitations of current treatment, the development of new agents for both HBV and HCV is urgently needed [21].

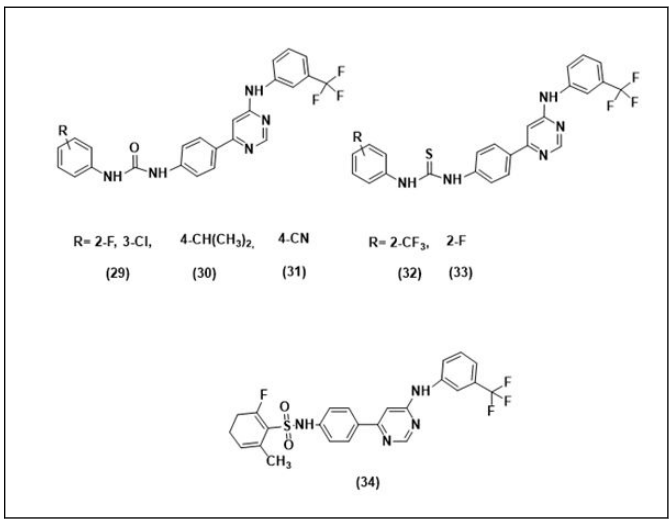
Described the synthesis and anti-HCV activity of a novel class of pyrimidine nucleosides with 40-carboxymethyl and 40-carboxamide functional groups. Among them, some of the compounds were discovered to be effective anti-HCV agents with no toxicity. The results showed that the anti-HCV activities of these compounds were superior to ribavirin (EC50=81.9 M). Among the fully synthesized compounds, 28 were discovered to be the most active analogue that interacts synergistically with ribavirin to inhibit HCV RNA replication [21].



Pyrimidines as anti-inflammatory agents

Inflammation is a feature of many diseasesand its persistence can lead to conditions such as sepsis, arthritis, atherosclerosis, diabetesand even cancer [22]. TNF- overexpression has been linked to a variety of serious inflammatory disorders, including rheumatoid arthritis, inflammatory bowel disease (IBD), hn's osteoarthritis and Crodisease. TNF is a powerful inducer of pro-inflammatory cytokines like IL-1, IL-6 and IL-8. As a result, agents that inhibit TNF- production can lower the levels of these pro-inflammatory cytokines, reducing inflammation and preventing further tissue destruction [23].

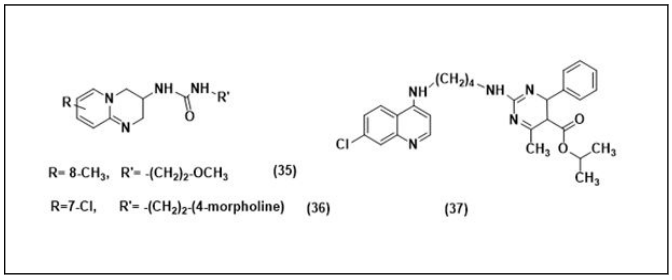
Used Suzuki cross-coupling, acid amination and reduction to create a class of pyrimidine derivatives. All of the synthesized compounds were tested for their ability to produce pro-inflammatory cytokines such as TNF and IL-6. Compounds 29, 30, 31, 32, 33 and 34 were discovered to be potent anti-inflammatory agents among all compounds tested. They demonstrated 48–78% TNF- and 56–96% IL-6 inhibitory activity when compared to standard dexamethasone at 10 μM [24].



Pyrimidines as anti-malarial agents

Malaria is caused by the parasite Plasmodium falciparum and is a major health concern in Africa, South America and many parts of Asia. Current therapies continue to rely on drugs that were developed decades ago. The genome sequencing of Plasmodium falciparum has revealed some new targets for drug and vaccine development. The development of newer antimalarial drugs is only an economically and environmentally viable alternative to combating the disease's threat. [25].

Synthesized and tested a series of pyrido[1,2-a]pyrimidin-4-ones for their ability to inhibit FP-2 in vitro. The studies identified Plasmodium falciparum cysteine protease falcipain-2 (FP-2) as a promising target for antimalarial chemotherapy and demonstrated that inhibiting this protease harms parasite growth. Compounds 35 and 36 were found to have excellent FP-2 inhibition and may serve as lead compounds for further research into potent FP-2 inhibitors as potential antimalarial drugs [25]. Singh et al. designed synthesized and characterized 4-aminoquinoline pyrimidines. All of the synthesized compounds were tested for antimalarial activity. Compound 37 was found to be the most active (IC50=156, 153, respectively) in the series against both CQS and CQR strains of *P. falciparum* [26].

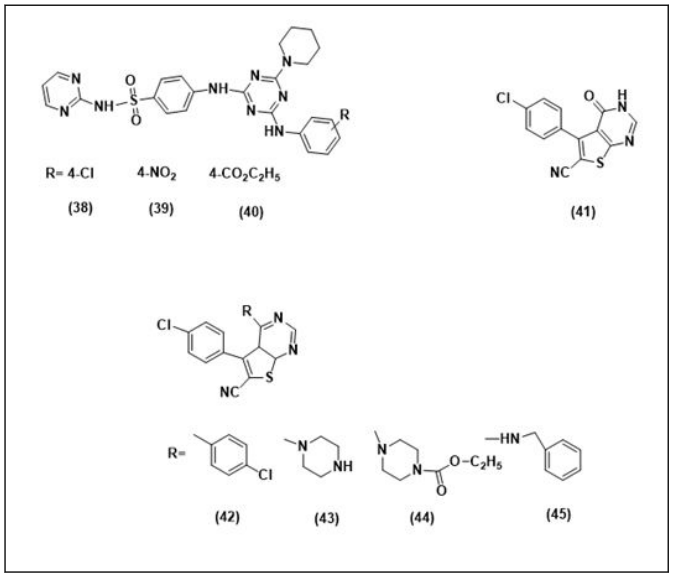


Pyrimidines as anti-microbial agents

Resistance to existing antimicrobial drugs is rapidly developing, posing a serious threat to public health. As a result, there is an urgent need to develop novel antimicrobial agents with potent antimicrobial activity against multidrug-resistant microorganisms [27].

Synthesized and tested a series of 4-(4-(arylamino)-6-(piperidin-1-yl)-1,3,5-triazine-2-ylamino)-N-(pyrimidin-2-yl) benzene sulfonamide analogues for *in-vitro* antimicrobial activity. Gram-positive bacteria [*S. aureus* (MTCC 96), *S. pyogenes* (MTCC 442)], Gram-negative bacteria [*E. coli* (MTCC 443), *P. aeruginosa* (MTCC 1688)] and fungal strains [*C. albicans* (MTCC 227), *A. niger* (MTCC 282), *A. clavatus* (MTCC 1323)] were tested. Compounds 38, 39 and 40 demonstrated significant antimicrobial activity against a variety of microbe strains [27].

Devised a series of thermally selective reactions to produce a class of 4-aminothieno[2,3-d]pyrimidine-6-carbonitrile derivatives. Using the broth microdilution method, all of the synthesized compounds were tested for antimicrobial activity against several bacteria, including *Staphylococcus aureus* MTCC-96, *Escherichia coli* MTCC-443, Pseudomonas aeruginosa MTCC-441, *Streptococcus pyogenes* MTCC-442 and fungi *Aspergillus niger* MTCC-282. Compounds 41, 42, 43, 44 and 45 demonstrated good antibacterial activity when compared to standard ampicillin, compounds 44 and 45 demonstrated superior antifungal activity when compared to griseofulvin [28].



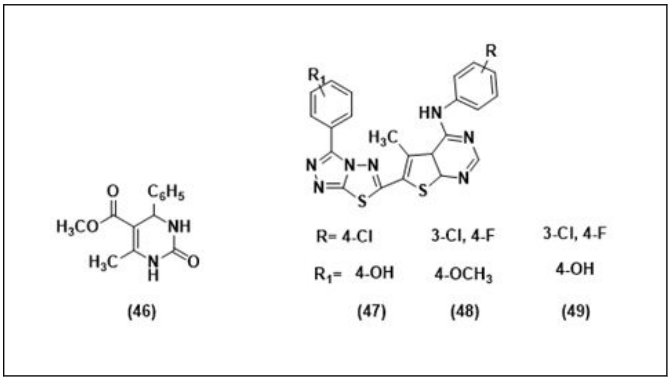
PYRIMIDINES AS ANTI-OXIDANT AGENTS

The overproduction of superoxide radicals by mitochondria plays an important role in the activation of other downstream path physiologic cycles involved in the production of reactive oxygen species (ROS) [33]. Furthermore, pyrimidine derivatives are effective antioxidants capable of neutralizing free radicals. As a result, antioxidants that forage reactive oxygen species may be extremely beneficial in preventing the onset and progression of oxidative diseases. The homeostatic balance between the

Reactive Oxygen Species (ROS) and endogenous antioxidants is essential for maintaining healthy tissues [29].

Developed an efficient catalytic method for producing 3,4-dihydropyrimidinones in high yield using a one-pot three-component Biginelli condensation with triethyl-ammonium acetate (TEAA) as a catalyst/reaction medium. The antioxidant properties of all the synthesized compounds were evaluated using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging and Cupric Reducing Antioxidant Capacity (CUPRAC) assays. Compound 46 demonstrated the highest absorbance (0.87) at 100 ppm in this assay when compared to standard gallic acid (1.4) and quercetin (1.2) at the same concentration. [30].

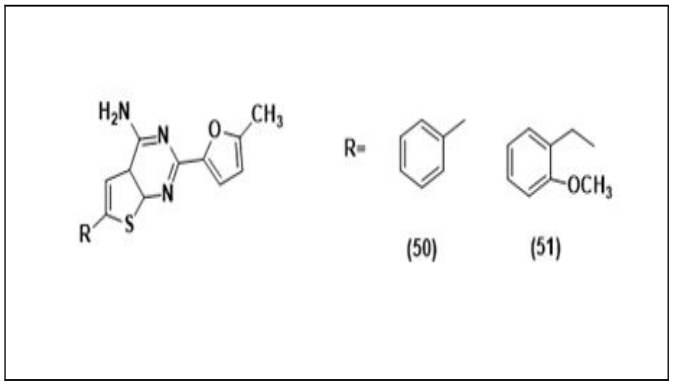
Designed, synthesized and characterized 1,2,4-(triazolo[3,4-b][1,3,4]thiadiazol-6-yl)selenopheno[2,3-d]pyrimidine analogues with substituted anilines and benzoic acids. DPPH, NO, and H2O2 radical scavenging methods were used to test the antioxidant activity of the newly synthesized compounds. Compounds 47, 48 and 49 were found as promising antioxidant molecules when compared with standard drugs Ascorbic acid and Butylated Hydroxy Toluene (12.27 ± 0.86 and 16.53 ± 1.74 respectively) with the least values of IC50 11.02 ± 0.27, 10.41 ± 0.23 and 9.46 ± 0.91 µg ml-1, inhibition concentration respectively. The study indicates that these compounds were capable of significant scavenging properties towards DPPH [31].



PYRIMIDINES AS ANTIPARKINSONIAN AGENT

Parkinson's Disease (PD) is a slowly progressive neurodegenerative disease characterized primarily by the selective loss of dopaminergic neurons in the Substantia Nigra (SN), affecting 1–2% of the general population over the age of 65. Adenosine is a neuromodulator that coordinates dopamine and other neurotransmitters involved in motor function, mood and memory. Selective A2A antagonists are a target for symptomatic relief in Parkinson's disease, and some reports suggest that they may also slow disease progression due to their neuroprotective activity [32].

Identified a novel series of benzyl substituted thieno [2,3-d] pyrimidines as potent A2A receptor antagonists. Some of the synthesized compounds were tested for their ability to reverse cataleptic activity in mice. In most cases, these compounds were tested in mice as a single oral dose of 3 or 10 mg/kg. Compounds 50 and 51 were discovered to be active at 10 mg/kg [32].



PYRIMIDINES AS ANTIPROTOZOAL AGENT

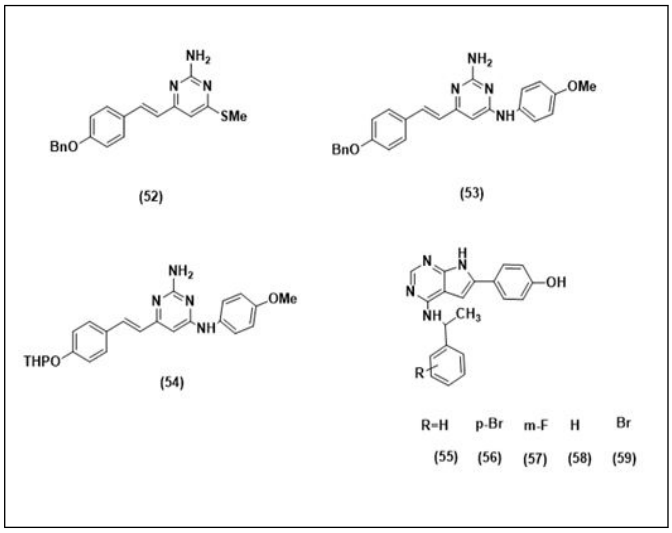
Malaria, dysentery, leishmaniasis and human African trypanosomiasis are all parasitic protozoa-caused diseases that are major causes of death worldwide. As a result, research into the effects of organic compounds on protozoa is critical [38]. Leishmaniasis is a parasitic disease transmitted by female phlebotomine sand flies that are caused by more than 20 species of the protozoan Leishmania.

The major clinical forms of leishmaniasis are Visceral Leishmaniasis (VL), Cutaneous Leishmaniasis (CL), and Mucocutaneous Leishmaniasis (MCL), which differ in immunopathologies as well as morbidity and mortality [33].

Created a library of substituted aryl pyrimidine derivatives. Eight of them had promising IC50 values ranging from 0.5 to 12.9 M. All of these compounds' Selectivity Indices (SI) was found to be higher than those of the reference drugs, Sodium Stibogluconate (SSG) and miltefosine.

These compounds were then tested *in vivo* for antileishmanial activity against the L. donovani/hamster model. Compounds 52, 53 and 54 inhibited parasitic multiplication significantly (88.4 %, 78.1 %, and 78.2 %, respectively) at a daily dose of 50 mg/kg i. p. for 5 days. Compound 52 could be a new lead that could be investigated as a potential antileishmanial agent [33].

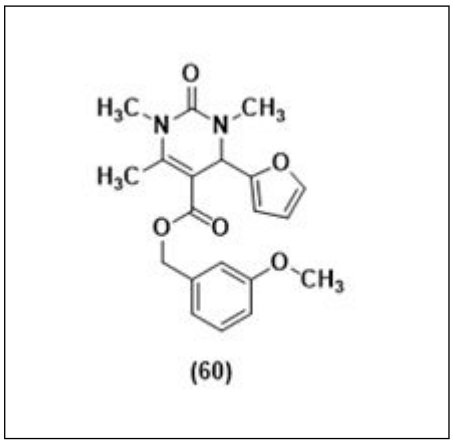
Used Tetrahymena as a model organism to design, synthesize and test 6-aryl-pyrrolo[2,3-d]pyrimidine-4-amines for antiprotozoal activity.
The protozoacidal activity results revealed that compounds 55, 56, 57, 58 and 59 were highly potent at dose concentrations ranging from 8-16 g/ml [34].



PYRIMIDINES AS ANTI-THYROID AGENTS

The sodium iodide symporter (NIS), a glycoprotein with 13 putative transmembrane domains, mediates iodide translocation into thyroid cells, which is the rate-limiting step in the biosynthesis of iodinated hormones T3 and T4. During lactation, these are primarily expressed in the thyroid gland and a few other tissues such as the salivary glands, gastric mucosa and mammary glands. Furthermore, the ability of NIS-expressing cells to absorb iodide has provided a foundation for extra-thyroid cancer cell destruction by radioiodine following tumor-selective NIS introduction [35].

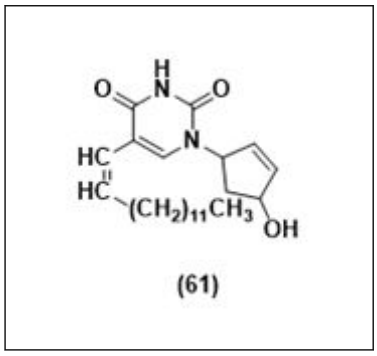
Used the multi-component Biginelli reaction to synthesize a small library of dihydro pyrimidin-2-ones (DHPMs), and the compounds were tested for their ability to block sodium iodide symporter (NIS) *via* a cell-based assay. Compound 60 gave the best results (IC50=65 pM). The research raises new hopes for the development of anti-thyroid medications [35].



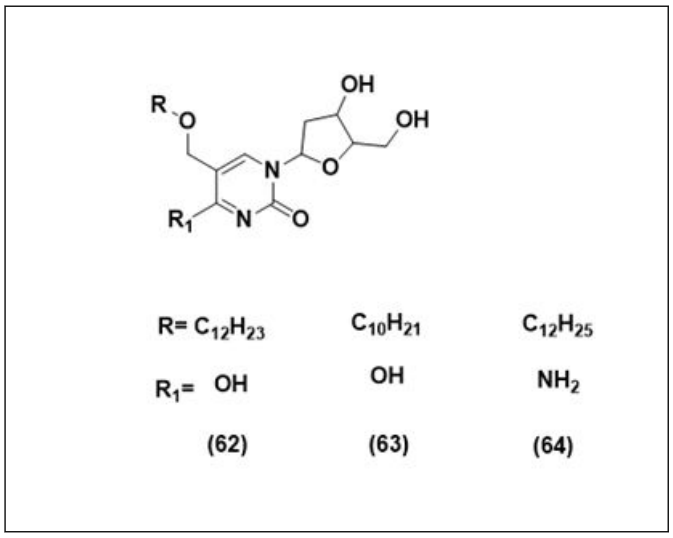
PYRIMIDINES AS ANTI-TUBERCULAR AGENTS

Tuberculosis is a chronic infectious disease spread by cough-propelled droplets containing the pathogenic bacterium Mycobacterium tuberculosis. Although most isolates of M. tuberculosis are killed by currently available drugs, strains resistant to each of these have emerged, and multiply resistant strains are becoming more common. Because of the growing problem of drug resistance, as well as the global incidence of several thousand new cases per year, there is an urgent need for new antituberculosis therapies [36].

Created and tested a new class of carbocyclic uracil derivatives for antituberculosis activity. Compound 61 exhibited the most potent antituberculosis activity against two Mycobacterium tuberculosis strains: laboratory sensitive (H37Rv) and MDR strain (MS-115) resistant to the top five antituberculosis drugs (isoniazid, rifampicin, streptomycin, ethambutol and pyrazinamide). Compound 61 had the same antituberculosis activity as a racemic mixture and as individual (+) and (-) enantiomers [37].



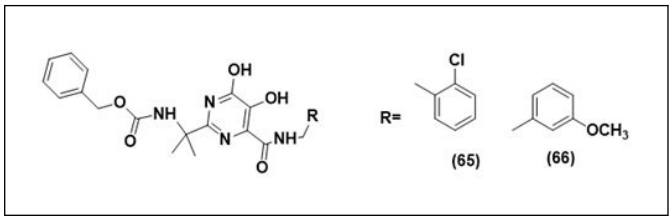
Reported the synthesis of C5 modified pyrimidine nucleoside derivatives and tested them for antituberculosis activity. 5-Dodecyloxymethyl-2'-deoxyuridine (62), 5-decyl to synthesize small triazolidomethyl-2'-deoxyuridine (63), and 5 and the compunds dodecyltriazolidomethyl-2'-deoxycytidine (64) inhibited the results growth of Mycobacterium tuberculosis strains-laboratory H37Rv (MIC=20, 10, and 20 g/ml, respectively) [38].



Pyrimidines as anti-viral agents

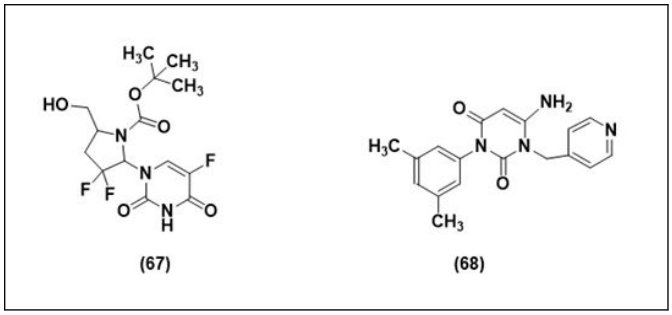
Synthesized and tested *in vitro* a small library of 5,6-dihydroxypyrimidines for their anti-HIV activity profile. Among the synthesized compounds, compounds 65 and 66 demonstrated significant anti-HIV activity, with EC50 values of

0.14 and 0.15 M, and TI (therapeutic index) values of >300 and >900, respectively. Thus, the study findings indicated that 5,6-dihydroxypyrimidines may serve as a lead compound for the discovery of potent anti-HIV agents due to their low cytotoxicity and high therapeutic index [39].

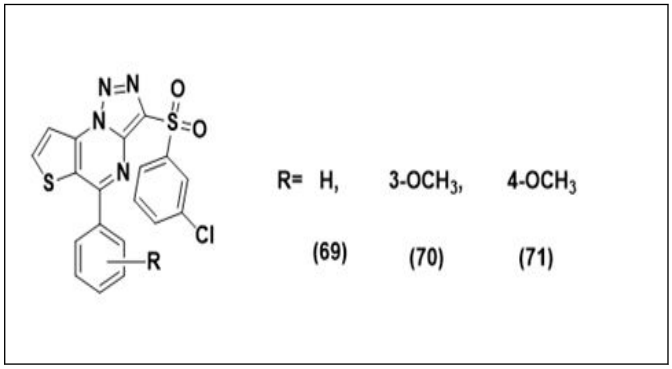


Synthesized and tested 20,30-dideoxy-20,20-difluoro-40-azanucleoside derivatives of both pyrimidine and purine nucleobases for anti-HIV-1 and anti-HCV activity. Among the compounds in the series, 40-azanucleosides 67 was found to be the most active (EC50=36.9 M), and none of the compounds was found to have anti-HCV activity [40].

Two new series of 4-aminopyrimido [4,5-b] indole ribonucleotide derivatives are described. Sakakibara et al. synthesized and tested a library of 3-(3,5-dimethylbenzyl) uracil analogues for non-nucleoside HIV-1 reverse transcriptase inhibition. 108 of these compounds were discovered to be effective against HIV-1 activity (EC50 =0.03 M and a high selectivity index=2863). As a result, compound 68 could serve as a starting point for further anti-HIV drug optimization [41].



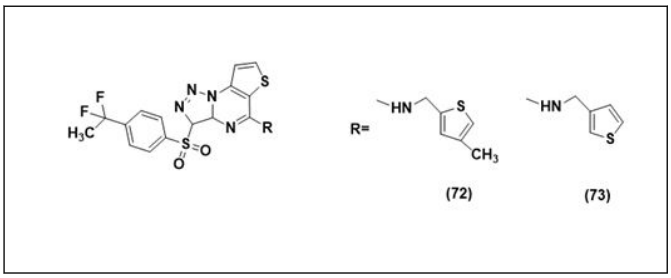
Discovered a class of Triazolothieno Pyrimidine (TTPM) compounds that are effective HIV-1 replication inhibitors. Using a cell-based full replication assay, it was discovered that the aryl-substituted TTPM derivatives 69, 70 and 71 exhibited significant inhibitory activity while maintaining acceptable safety margins [42].



PYRIMIDINES AS HUMAN UREA TRANSPORT PROTEIN (UT-B) INHIBITORS

In order to create concentrated urine, Urea transporters (UTs) in the kidney are required. Epithelial cells in some kidney tubules express UT-A proteins encoded by the SLc14A2 gene, while endothelial cells in some micro vessels express UT-B encoded by the SLc14A1 gene. The original compounds had limitations such as poor metabolic stability and activity against rodent UT-B. As a result, additional research is required for the development of UT-B inhibitors.

Designed and synthesized some UT-B inhibitor analogues based on previously synthesized triazolothienopyrimidine derivatives that were previously reported as UT-B inhibitors. All of the compounds that were synthesized met the structural requirements for potency and microsomal stability to function as UT-B inhibitor scaffolds. Two compounds, 72 and 73, were discovered to have nanomolar inhibitory potency (IC50=40 nM).[43]



CONCLUSION

This study sheds light on pyrimidine derivatives and their various applications in drug development and medicine. As highlighted in this review, pyrimidine derivatives have been investigated for a variety of ailments. Pyrimidines are structural components of important biomolecules such as DNA and many biologically relevant drugs. Pyrimidine derivatives are gaining popularity as antimicrobial, anticancer, antiviral, anticonvulsant and other agents. Furthermore, due to the resistance of currently available drugs, there is a strong need for additional pyrimidine research. This review could help in exploring the newer pyrimidine analogues with improved biological potency.

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