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Review Article

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Focused Insights Into Emerging Pyrimidine Molecules with Multifarious Anti-Infective Perspectives

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ABSTRACT

Over the past 60 years, pyrimidines have grown in importance as a fundamental structural component of many therapeutic compounds. This article reviews the recent anti-infective (antibacterial, antifungal, and antiviral) activities where pyrimidines have played a significant role in drug discovery. In addition to presenting the medicinal agents' synthesis, the essay emphasizes the significance of the biological target in relation to the illness model. Furthermore covered are the pharmacokinetics and pharmacodynamics, biological potency, and ADME characteristics. This survey aims to illustrate the medicinal chemistry features of pyrimidine as a bioisostere for phenyl and other aromatic π systems, as well as the efficacy and affinity of pyrimidine-based medicines. The purpose of this article is to may help researchers who are thinking about using the pyrimidine scaffold as chemotype in future therapeutic candidates to treat diseases that were thought to be incurable.

Keywords: Pyrimidine, Inhibitors, Synthesis, Antibacterial, Antifungal, Antiviral

INTRODUCTION

Pyrimidine is an important electron-rich aromatic heterocycle that plays a crucial role as a component of DNA and RNA. The human body relies on it as a vital component.[1] The pyrimidine framework is extensively utilised in many therapeutic applications owing to its facile synthesis and versatile structure. These uses encompass the treatment of infections, malaria,[3] viral illnesses, cancer, leishmaniasis, inflammation, pain, seizures, hypertension, and oxidative stress.[2,3,4,5,6-11] Furthermore, pyrimidines have demonstrated potential therapeutic properties that are particularly important for medications that act on the central nervous system (CNS), calcium channel blockers, and antidepressants. Pyrimidines have attracted considerable attention from organic and medicinal chemists because of their wide-ranging biological activities. The pyrimidine framework has the benefit of being easily obtainable and may be conveniently modified to achieve a variety of structural changes at positions -2, -4, -5, and -6 **(Figure 1)**.

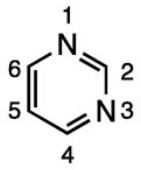

Figure 1: Structure of pyrimidine.

Figure 2 displays a selection of commercially available medications that are based on pyrimidine. The pyrimidine ring's capacity to engage with different targets through the formation of hydrogen bonds and its propensity to behave as bioisosteres for phenyl and other aromatic π systems typically enhance the drug's pharmacokinetic/pharmacodynamic features. The pyrimidine ring possesses distinctive physiochemical characteristics, which have resulted in its extensive utilization in therapeutic candidates exhibiting a wide range of actions. The number of medications based on this specific molecular structure has grown rapidly in the field of pharmaceuticals, targeting a diverse range of biological objectives with varying treatment needs.

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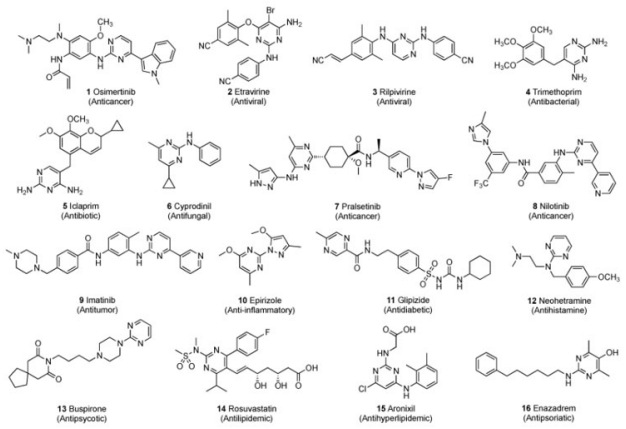

Figure 2: Marketed drugs containing the pyrimidine scaffold.

The objective of this review paper is to offer a comprehensive survey of the synthetic techniques employed in the production of pyrimidine derivatives, together with the significant biological and clinical significance of these systems in various therapeutic contexts. The drug candidates in this analysis are categorised based on the specific medical problems they are designed to treat, including bacterial, fungal, and viral infections. The review covers the literature from the past two years. The abundance of research papers produced in a relatively brief period of time highlights the importance and potential of pyrimidine-based molecules in medicinal research. The publication compares the effects of various commercial and experimental drugs with those of newly developed drug prototypes.

PYRIMIDINE-BASED DRUGS FOR TREATMENT OF INFECTIONS

Antibacterial activity

Researchers have concentrated their efforts on creating a primary compound to combat tuberculosis (TB), a deadly contagious illness caused by *Mycobacterium tuberculosis* that is widespread in Asia and Europe.[12] While the present treatment approach for this illness utilizes a combined regimen that is highly efficacious, resistance to this treatment option has begun to appear. Hence, it is imperative to create a potent antitubercular chemical that operates through a unique mechanism to combat drug-resistant tuberculosis. The scientists observed that Certinib, a medication licensed for treating anaplastic lymphoma kinase, exhibited antitubercular characteristics when tested using a phenotypic screening method. The chemical had a moderate minimum inhibitory concentration (MIC) of 9.0 µM/mL against the H3Ra variant. The researchers in this study successfully determined the primary pharmacophore and promptly established a structure-activity relationship (SAR) for this group of chemicals. The methodology used to create model molecules for this investigation is illustrated in **Figure 3**. The compound 2,4,5-trichloropyrimidine **(17)** underwent a nucleophilic aromatic substitution (SNAr) reaction at position C4 with the commercially available compound 2-isopropoxy-5-methyl-4-(piperdin-4-yl) aniline **(18)** in the presence of *N*,*N*-diisopropylethylamine (DIPEA) in isopropanol at a temperature of 80°C. This reaction yielded compound **(19)**. Compound **(19)** underwent additional substitution by anilines at C2 in the presence of acid, resulting in the formation of compound **(20)**. Ammonolysis of compound **(19)**, followed by the removal of the tert-butoxycarbonyl (Boc) protecting group from the nitrogen atom using trifluoroacetic acid (TFA) in dichloromethane (DCM), resulted in the formation of compound **(21)**. Ultimately, the Suzuki-Miyaura coupling of compound **(19)** with an arylboronic acid was achieved using [1,1'-bis (diphenylphosphino) ferrocene] dichloropalladium (II) (Pd(dppf) C_{l2}) in the presence of cesium carbonate (Cs_2CO_3) as the base. This reaction took place in aqueous dioxane under reflux conditions. Subsequently, the Boc protecting group was removed, resulting in the desired products **(22)**.

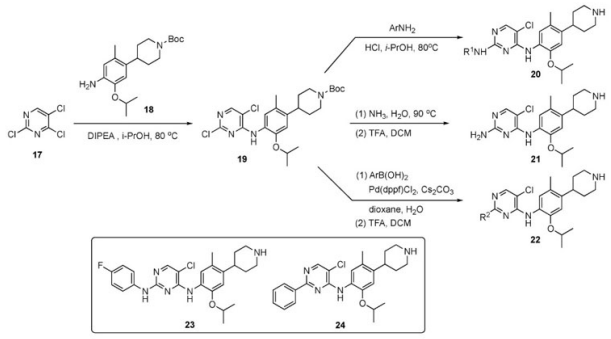

Figure 3: Development of pyrimidines.

This report describes a total of 58 compounds, and the publication emphasizes the biological importance of these pharmacological molecules. Compounds **(23)** and **(24)** had little effectiveness against multidrug-resistant *Staphylococcus aureus* (MRSA), *Mycobacterium abscessus*, and *Mycobacterium smegmatis*, with minimum inhibitory concentration (MIC) values ranging from 4 µg/mL to 8 µg/mL. Drug candidate **(24)** had strong efficacy against the H37Ra (ATCC 25177) and H37Rv (ATCC 27294) strains of tuberculosis, as well as drug-resistant variations found in clinical settings, with minimum inhibitory concentration (MIC) values ranging from 0.5 to 1.0 µg/mL. This chemical also demonstrated satisfactory *in vivo* toxicity, even at a high oral dose of 800 mg/kg. The pharmacokinetic (PK) characteristics of **(24)** were assessed in Sprague–Dawley rats. Compound **(24)** showed moderate exposure with a maximum concentration (C_{max}) of 592±62 mg/mL, delayed elimination with a half-life ($t_{1/2}$) of 26.2±0.9 hrs, a low clearance (CL) value of 1.5±0.3 L/h/kg after intravenous (i.v.) injection, and promising oral bioavailability (F) with a value of 40.7%.[13]

In their study, the research group investigated the potential of pyrimidines as anti-infective agents targeting *M. tuberculosis*.[14] Tuberculosis (TB) is a contagious illness that mostly affects the lungs and other organs, including the spine, kidney, and brain. It cycles between active and latent stages and poses a challenge to the immune system's defense mechanism.[15] The prevalence of multidrug-resistant (MDR) strains of this disease is increasing for isoniazid and rifampicin, which are the primary medications used as the first line of defense. This work aimed to suppress the growth of *M. tuberculosis* by specifically targeting the fatty acid production pathway of the infection. Their focus was primarily on acyl carrier protein reductase, a crucial element of the mycobacterial survival route. When this pathway is disrupted, the bacteria are deprived of nutrients, leading to the death of their cells and the complete elimination of TB. The intended library of chemicals was designed using the notion of molecular hybridization in this study.[16]

A number of model compounds were synthesized using the generalized method described in **Figure 4**. The synthesis commenced by conducting a one-pot multi-component reaction involving benzaldehydes **(25)**, ethyl cyanoacetate, thiourea, and potassium bicarbonate ($KHCO_3$) in ethanol. This reaction yielded pyrimidine derivatives **(26)**. The thiol **(26)** was subjected to hydrazinolysis using hydrazine hydrate in ethanol under reflux conditions, resulting in the formation of the 2-hydrazinyl-6-oxo-4-aryl-1,6-dihydropyrimidine-5-carbonitriles **(27)**. The compounds were then combined with isatin derivatives **(28)** in ethanol solution with small amounts of acetic acid to form the isatin-pyrimidine hybrids **(29)**.

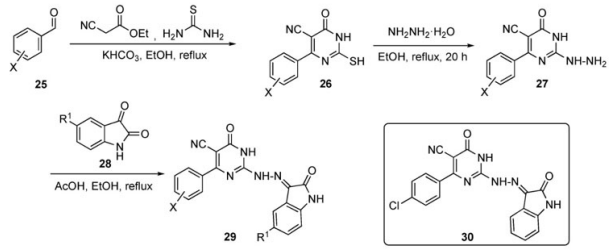

Figure 4: Synthesis of isatin–pyrimidine hybrids.

Compound **(29)** was tested for its inhibitory effect against three strains of TB, which included a sensitive strain (ATCC 25177 = H37Ra) and an isoniazid-resistant strain (ATCC 35822). Several of the potential derivatives exhibited a minimum inhibitory concentration (MIC) of less than 1 µg/mL against both strains, including the multidrug-resistant (MDR) and highly drug-resistant (XDR) strains. Among all the derivatives, compound **(30)** demonstrated the highest level of inhibition against MDR and XDR *M. tuberculosis*, with minimum inhibitory concentrations (MICs) of 0.48 and 3.9 µg/mL, respectively. However, the same drug had the highest potency against inhibin subunit alpha (InhA) with a half maximum inhibitory concentration (IC_{50}) of 0.6±0.94 µM. The authors achieved successful co-crystallization of compound **(30)** within the ligand-active region of InhA in this study.

A research group has recently focused on enhancing the effectiveness of Linezolid, a broad-spectrum antibiotic, by incorporating a pyrimidine ring into its structure.[17] Oxazolidinone ring cores are recognized for their strong efficacy against Gram-positive infections in the field of antibacterial agents, particularly.[18] Continuous enhancement of present drugs is necessary to develop next-generation antibiotics due to the widespread resistance exhibited by bacteria. The authors aimed to identify antibiotic candidates with additional antibiofilm properties, primarily targeting urinary tract infections. The scientists postulated that the incorporation of a pyrimidine moiety into the linezolid structure would enhance the drug's capacity to establish hydrogen bonds and increase the compound's permeability.

Figure 5 depicts the synthesis of a pyrimidine-linked prototype from the piperazine-linezolid precursor **(31)**, which was prepared using a previously established method.[19] Compound **(31)** reacted selectively with several 2,4-dichloropyrimidine derivatives **(32)** in the presence of triethylamine (TEA) in ethanol to produce intermediates **(33)**. The individual intermediates were subjected to further reactions with different amines in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH•H_2O) in ethanol, under mild acidic conditions. This resulted in the displacement of the C4 chloride from the pyrimidine ring and the formation of the desired pyrimidine-Linezolid structures **(34)**.

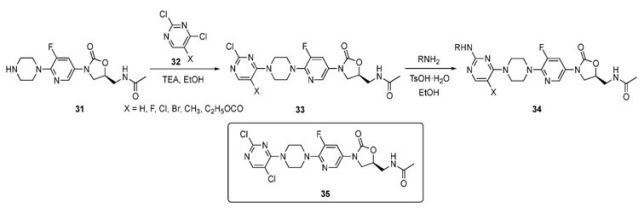

Figure 5: Synthesis of pyrimidine-appended Linezolids.

A total of 34 compounds were assessed for their antibacterial efficacy against seven distinct strains of mostly Gram-positive bacteria, namely *S. aureus*, *Enterococcus faecalis*, *S. pneumoniae*, *S. xylosus*, *Bacillus subtilis*, and *Listeria monocytogens*. Some derivatives had significant action against a specific group of these organisms, with **(35)** of them showing a MIC of 0.25-1 µg/mL against all of these pathogens. Candidate **(35)** exhibited a minimum inhibitory concentration (MIC) of 1 µg/mL against methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) bacteria. In addition, **(35)** exhibited a minimal biofilm inhibitory concentration (MBIC) that varied from 0.5–4 µg/mL against four bacterial strains, namely MRSA,

VRE, linezolid-resistant *S. aureus*, and linezolid-resistant *S. pneumoniae*. The authors have concluded that compound **(35)** has significant potential for further development as an antibacterial medication based on these data.

Researchers. aimed to create an antibacterial substance by integrating pyrimidines. They targeted the bacterial topoisomerase-II enzyme DNA gyrase.[20] DNA gyrase is the enzyme responsible for the processes of DNA replication, transcription, repair, and decatenation in bacteria. The gyrase consists of two subunits, namely gyrase-A and gyrase-B. One of these subunits regulates ATPase activity, while the other subunit functions by cleaving and rejoining bacterial DNA. DNA gyrase is responsible for preserving the structure of bacterial DNA, making it a prime candidate for the development of antibiotics.[21,22]

A research group developed a method to synthesize a group of pyrimidine-piperazine hybrids that are substituted with chrysin. This synthesis approach is illustrated in **Figure 6**. At first, 4,6-dihydroxy-2-methylpyrimidine **(36)** was synthesized by combining acetamidine hydrochloride and diethyl malonate with sodium acetate (NaOAc) in methanol. The hydroxyl groups in compound **(36)** were converted to chlorides using phosphorus oxychloride ($POCl_3$), resulting in the formation of dichloropyrimidine **(37)**. Subsequently, chrysin **(38)** underwent a nucleophilic aromatic substitution (SNAr) reaction with compound **(37)** in the presence of potassium carbonate (K_2CO_3) as a base and N,N-dimethylformamide (DMF) as a solvent, leading to the formation of compound **(39)**. The piperazinyl derivatives underwent a nucleophilic substitution reaction with **(39)** in the presence of DIPEA in ethanol, resulting in the formation of targets **(40)**.

The synthesized compounds were assessed for their activity against twelve distinct bacterial strains and two fungal species. The compounds displayed moderate antibacterial and antifungal effects, with the exception of **(41)**, which showed a MIC of 6.5 µg/mL against *Escherichia coli* and a significant antifungal MIC of 250 µg/mL against *Candida albicans*.

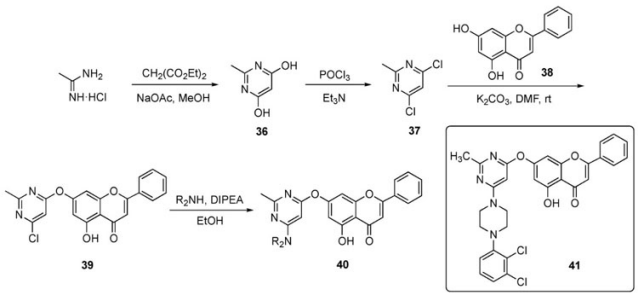

Figure 6: Synthesis of chrysin-based pyrimidine–piperazine hybrid.

Antifungal activity

In their invention, researchers aimed to create a novel category of anti-infective agents that are both safe and non-toxic. These compounds were specifically designed to combat various fungal infections, such as *C. parapsilosis*, *C. albicans*, and *S. cerevisiae*.[23] The patent details the process of synthesizing and assessing several pyrimidine derivatives from aryl sulfonamides **(42)** by their reaction with ethyl chloroformate using K_2CO_3 in acetone. This reaction yields the arylsulfonylurethane **(43)**, as depicted in **Figure 7**. Sulfonylureas **(44)** were generated by further reacting **(43)** with different substituted 2-aminopyrimidines. The patent results show that certain model compounds demonstrated antifungal activity that was either equivalent to or up to five times more than the recognized drug Amphotericin B. Additionally, the minimum inhibitory concentration (MIC_{90}) of several of these compounds, including compound **(45)**, revealed three to thirty times stronger activity than fluconazole. The drug prototypes demonstrated potent antifungal activity against multiple strains of *S. cerevisiae*, *C. albicans*, and *C. parapsilosis*. Compound **(45)** showed strong effectiveness against *C. albicans* in RPMI 1640, YNB, and YPD medium, with the most encouraging minimum inhibitory concentration (MIC_{90}) ranging from 0.05 to 0.3 µg/mL. Additionally, it demonstrated promising efficacy with a minimum inhibitory concentration (MIC_{90}) of less than 0.05–0.1 µg/mL against fluconazole-resistant strains of *C. albicans*, *C. parapsilosis*, and *S. cerevisiae*. The majority of the compounds examined in this series exhibited enduring antifungal action that remained unchanged even after a period of 72 hrs.

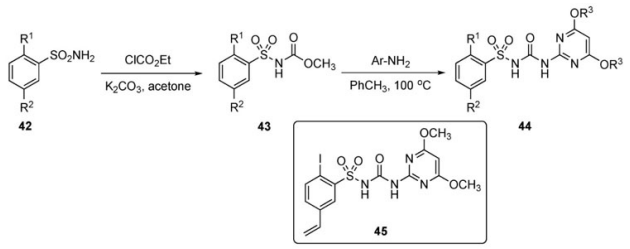

Figure 7: Synthesis of antifungal pyrimidine.

Antiviral activity

Researchers conducted a noteworthy study on pyrimidines as pharmacological frameworks for anti-infectives, specifically focusing on acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV).[24] Due to the introduction of antiretroviral medication, the categorization of HIV has shifted from a fatal illness to a controllable long-term condition. The scientists' primary objective was to create non-nucleoside reverse transcriptase inhibitors (NNRTIs), a class of antiviral medicines. The first-generation and second-generation NNRTIs were ineffective against mutant

strains, leading to significant drug resistance. The mutant strains K103N and Y181C emerged as a result of the use of first-generation medications, while the E138K mutation occurred in response to second-generation treatments.[25,26] In addition, the newer compounds exhibited restricted solubility profiles, leading to reduced bioavailability. Therefore, it was crucial to develop novel architectures with enhanced adsorption, distribution, metabolism, and excretion (ADME) characteristics as potential candidates for antiviral medications. The final desired compounds were synthesized in a single step from the previously published compounds, as illustrated in **Figure 8**. The Suzuki-Miyaura coupling reaction was performed using arylboronic acids **(46a-c)** in the presence of tetrakis (triphenylphosphine) palladium (0) ($Pd(Ph3P)_4$) and K_2CO_3 in DMF at a temperature of 100°C. This reaction yielded the compounds **(47)**, which were used as candidates for this investigation.[27]

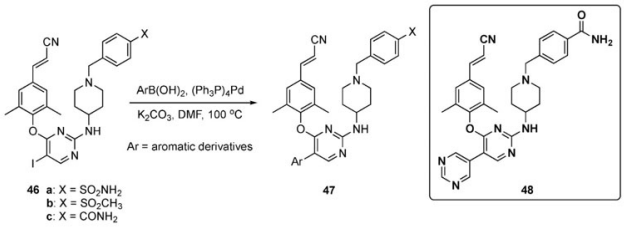

Figure 8: Synthesis of NNRT inhibitor pyrimidines.

A summary was compiled for **(39)** compounds that were synthesized and assessed. The screening revealed that the majority of the compounds demonstrated antiviral activity against the HIV-1-IIIB strain, with a half maximum effective concentration (EC_{50}) of less than 10 nM. This activity was compared to that of Etravirine, which had an EC_{50} of 3.5 nM. The majority of compounds demonstrated activity against the double mutant strain RES056 (K103N/Y181C) with an EC_{50} of 50 nM. Compound **(48)** exhibited the most potent EC_{50} values ranging from 3.43nM to 11.8 nM against a panel of wild type (WT) and resistant mutants. Significantly, compound **(48)** had the greatest effectiveness against K103N and Y188L, with EC_{50} values of 4.77 nM and 15.3 nM, respectively. From the perspective of drug absorption, distribution, metabolism, and excretion (ADME) and toxicology, **(48)** showed no inhibition of cytochrome P450 (CYP_{450}) enzymes (IC_{50}> 10 µM) and exhibited a favourable pharmacokinetic (PK) profile. The chemical exhibited a clearance of 82.7±1.97 mL/h/kg (slightly elevated) after intravenous (i.v.) injection of 2 mg/kg. It also shown a satisfactory oral bioavailability (F) of 31.8% when administered orally (p.o.) at a dose of 10 mg/kg. Ultimately, the compound **48** showed no signs of immediate harmful effects on Kunming mice, even at the highest tested dosage of 2000 mg/kg.

Researchers aimed to create a novel medication targeting the HIV-1 reverse transcriptase (RT) to combat AIDS.[28] RT has a crucial biochemical role in the replication of viral DNA/RNA-dependent DNA polymerase and ribonuclease.[29] At present, RT inhibitors are primarily categorised into two groups: nucleoside RT inhibitors (NRTIs) and non-nucleoside RT inhibitors (NNRTIs).[27] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have played a crucial role in highly active antiretroviral therapy because of their favourable anti-HIV-1 characteristics, precise targeting, and relatively minimal harm to the body. The authors of this study highlight the importance of developing new non-nucleoside reverse transcriptase inhibitors (NNRTIs) that are more effective against treatment-resistant strains of HIV-1 and have better pharmacological characteristics.

Figure 9 displays the synthesis of the potential chemicals for this study. The reaction involved the combination of nitroaryl halides **(49a-c)** with Boc-piperazine in the presence of K_2CO_3 in DMF at a temperature of 120°C, resulting in the formation of compound **(50)**. The adducts were transformed into the initial precursor through reduction to the aniline derivatives **(51)** using hydrogen gas and palladium on carbon catalyst in methanol. In order to synthesize the second precursors, the compound 2,4-dichloropyrimidine **(52)** was reacted with cyanophenols **(53)** (a: 4-hydroxy-3,5-dimethylbenzonitrile or b: (*E*)-3-(4-hydroxy-3,5-dimethylphenyl)acrylonitrile) using K_2CO_3 in DMF as a catalyst, resulting in the formation of compound **(54)**. Ether **(54b)** underwent Buchwald–Hartwig coupling with **(51)** using palladium acetate ($Pd(OAc)_2$), 3,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos), and Cs_2CO_3 in dioxane, resulting in the formation of **(55b)**. The Boc protecting group of compound **(55b)** was removed using trifluoroacetic acid (TFA) in dichloromethane (DCM), resulting in the formation of compound **(56b)**. This compound was then subjected to acylation or sulfonation at the nitrogen atom of the piperazine ring to obtain the desired final products, compound **(57b)**.[30]

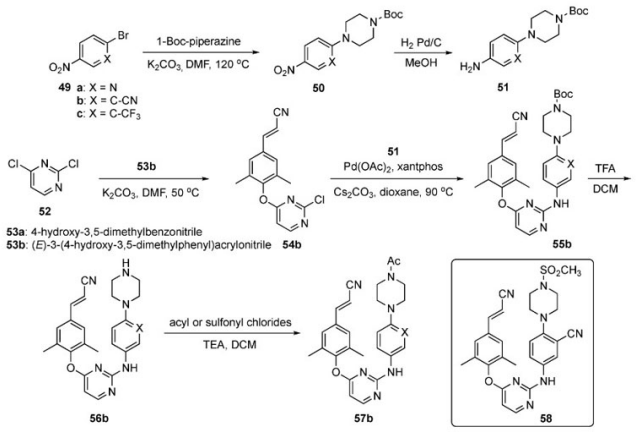

Figure 9: Synthesis of RT inhibitor pyrimidines.

Remarkably, out of the recently created compounds, **(58)** exhibited a substantial enhancement in their ability to combat HIV-1 strains when compared to the well-known NNRTI BH-11c. In addition, **(58)** exhibited extremely high efficacy (0.1–2.6 nM) against wild-type and five mutant strains of HIV-1, namely K103N, L100I, E138K, F227L/V106A, and Y181C. Additional molecular dynamics simulations were performed to elucidate the disparities in inhibitory efficacy between compound **(58)** and Etravirine **(2)** against reverse transcriptase (RT) variations. Candidate **(58)** exhibited enhanced water solubility (13.46 µg/mL at pH 7.0) in comparison to 2 (<1 µg/mL at pH 7.0), while maintaining a ligand efficiency (LE) value of 0.32. Furthermore, compound **(58)** exhibited markedly reduced inhibitory activity compared to compounds **(2)** and rilpivirine **(3)** against CYP2C9, suggesting that **(58)** is less prone to causing drug-drug interactions.[31]

Compound **(58)** underwent PK evaluation in a Sprague-Dawley rat model. It exhibited a satisfactory half-life ($t_{1/2}$), moderate clearance, and a favorable distribution volume after receiving an intravenous (i.v.) dose of 2.0 mg/kg. When given orally at a dosage of 10.0 mg/kg, **(58)** individuals had a low maximum concentration (Cmax) and a concentration-time curve (AUC) that indicated poor results. However, the oral bioavailability (F) of compound **(58)** was found to be 1.34%. Therefore, unless more improvements are made, the scientists identified **(58)** as a highly promising lead chemical that deserves further investigation.

Researchers have attempted to enhance the efficiency of a pyrimidine-based pharmacological framework for specifically targeting the influenza virus.[30] Influenza is a contagious illness that affects the respiratory system and causes more than 300,000 deaths annually worldwide. This places a significant social and economic burden on society.[31] An effective method to reduce this burden is to utilize the influenza vaccine, however, the vaccine's efficacy is sometimes compromised due to antigenic drift and a lack of alignment with the circulating strains. Neuraminidase inhibitors (such as oseltamivir) and RNA polymerase (RNAP) inhibitors (such as baloxavir) are commonly used as the first line of defense drugs. However, due to the development of resistant mutations, there is a need to create new antiviral drugs that directly target these mutations and to discover new drugs with unique mechanisms of action.[32] The researchers presented a medicinal chemistry approach to attach aza-β3- or β2,3-amino acids to a 7-azaindole ring on the RNAP component PB2. This subunit is considered an excellent target for the development of antiviral drugs. By taking advantage of easy structural modification, a variety of aza-β-amino acid patterns with different sizes, shapes, steric hindrances, and configurations were connected to a pyrimidine and examined for their effectiveness against viruses.

Figure 10 illustrates the process of synthesizing experimental chemicals, which begins with 2,4-dichloro-5-fluoropyridine **(59)**. After replacing the compound at position C4 with ethyl *N*-amino-*N*-(alkyl)glycinates**(60)** using DIPEA in THF, the resulting intermediates **(61)** were then combined with azaindoleboronic acids **(62)** using Suzuki-Miyaura coupling. This reaction was carried out using $(Ph_3P)_4Pd$ and K_2CO_3 in a mixture of water and acetonitrile (ACN). The final product obtained from this reaction was compound **(63)**. The structure underwent hydrolysis using lithium hydroxide (LiOH) in an aqueous solution of tetrahydrofuran (THF) to produce the intended acid targets **(64)**.[32]

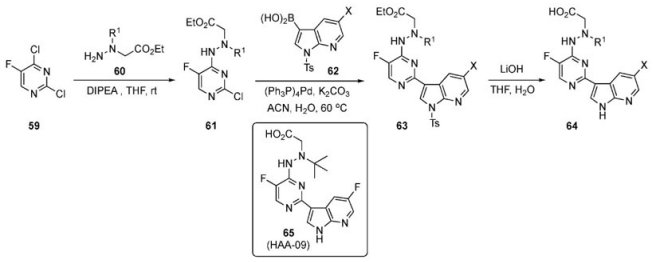

Figure 10: Synthesis of azaindole-linked pyrimidine.

The tests conducted on these compounds demonstrated that compound **(65)** (HAA-09) effectively targets the influenza PB2_cap binding domain, exhibiting strong anti-influenza viral effects in both laboratory and animal models. This drug candidate exhibited potent inhibition against the polymerase of the influenza A virus and demonstrated activity at concentrations below one micromolar, with an IC_{50} of 0.06 µM and an EC_{50} of 0.03 µM. Compound **(65)** demonstrated enhanced antiviral efficacy against both the oseltamivir-sensitive A/WSN/33 and oseltamivir-resistant H275Y genotypes. The compound exhibited no inhibition of the human ether-á-go-go related gene (hERG) channel, indicating a minimal risk for hERG-associated cardiac repolarization (measured using manual patch technique, IC_{50}> 10 µM) and a prolonged plasma stability (half-life > 12 hr). Furthermore, a subacute toxicity investigation was conducted in healthy mice to evaluate the safety profiles *in vivo*. Lead compound **(65)** exhibited a positive safety profile when given orally to healthy mice at a high dosage of 40 mg/kg, once daily for a duration of three days. The pharmacodynamics (PD) analysis of orally administering the treatment to individuals showed a viral load reduction of almost 2 logarithmic units and a survival advantage in a mouse model of deadly infection. The significant decrease in the quantity of influenza A virus in the lungs of infected mice provided confirmation that **(65)** had a direct impact on the propagation of the virus. Considering these findings, structure **(65)** was deemed a promising PB2 inhibitor that can be further explored for the development of anti-influenza drugs.[33]

CONCLUSION

The application of molecular dynamics modeling and the accumulation of knowledge have uncovered multiple novel structures capable of interacting with crucial enzymes that play a significant role in the development of various debilitating illnesses. Given the abundance of available precursors, it should be relatively easy to obtain pyrimidine medicines that are expected to bind with these enzymes for the purpose of screening. Several pyrimidines mentioned have displayed IC_{50} values within the nanomolar range, had favorable ADME features, and demonstrated compelling pharmacokinetic/pharmacodynamic readouts, making them promising candidates for novel drugs targeting diverse health issues. The increased efficacy of these substances should result in reduced dosage requirements, leading to a decrease in the occurrence of adverse effects compared to existing medications. Pyrimidine-based medications possess significant efficacy and demonstrate a notable ability to avoid off-target toxicity, such as hERG, ion-channel, CYP_{450} inhibition and induction, and cytotoxicity towards normal cell lines. This characteristic establishes a safety margin for their utilization. Many of the most powerful prototype chemicals had minimal toxicity in animal testing, suggesting that this may also be the case in humans. In addition, this article discusses various potential molecules that have shown indications of pyrimidines hybridizing with different ring systems. These molecules have demonstrated the ability to effectively address the growing challenges of drug resistance. While pyrimidines were previously utilized as anti-infective and anticancer agents, recent findings have revealed new applications for this ring structure. The research presented in this review aims to persuade the reader about the significant potential of targets constructed based on the pyrimidine core ring structure. In general, pyrimidine-based medicines and hybrid structures show great potential as new therapeutic agents. Pyrimidines are currently a crucial component in many existing therapeutic drugs. However, their significance is expected to grow even further as the need for new treatments increases to ensure the well-being of the worldwide population.

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Conflict of interest

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Suman Uraiha: Editing, Literature Review

Lata Patel Choudhary: Concept, Checking

Yogesh Pounikar: Revisions

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