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Synthesis, Structure Activity Relationship and Pharmaceutical Applications of Pyrimidine Analogues: A Review

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ABSTRACT

Pyrimidine and its analogues are important heterocyclic compounds that have various applications in chemistry and pharmacy. These compounds are composed of a six-membered ring containing four carbon atoms and two nitrogen atoms, which are arranged in a planar fashion. Pyrimidine is a fundamental building block of nucleic acids such as DNA and RNA and plays a critical role in cellular metabolism. Pyrimidine analogues have attracted significant attention from chemists and pharmacologists due to their diverse biological activities, such as antiviral, antibacterial, anticancer, and anti-inflammatory properties. In this article, we provide an overview of the chemical structure, synthesis, and biological applications of pyrimidine and its analogues. We also discuss various classical and modern methods for the synthesis of pyrimidine analogues, including transition-metal-catalyzed reactions, click chemistry, and microwave-assisted reactions. The diverse range of biological activities exhibited by pyrimidine analogues has led to the development of numerous pyrimidine-based drugs, including anticancer agents such as 5-fluorouracil and capecitabine, and antiviral drugs such as acyclovir and ribavirin. The synthesis and biological applications of pyrimidine and its analogues are of great interest to chemists and pharmacologists, and they continue to be an active area of research.

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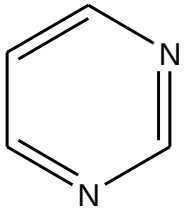
1. INTRODUCTION:

Pyrimidine and its analogues are an essential class of heterocyclic compounds that have found numerous applications in chemistry and pharmacy. These molecules are composed of a six-membered ring containing four carbon atoms and two nitrogen atoms, which are arranged in a planar fashion (Obaid RJ, *et. al.,* 2022). Pyrimidine is a fundamental building block of nucleic acids such as DNA and RNA, and it plays a critical role in cellular metabolism. Pyrimidine derivatives and analogues have attracted significant attention from chemists and pharmacologists due to their diverse biological activities, such as antiviral, antibacterial, anticancer, and anti-inflammatory properties (Mukherjee AK, *et. al.,* 2001). This has led to the development of numerous pyrimidine-based drugs, including anticancer agents such as 5-fluorouracil and capecitabine, and antiviral drugs such as acyclovir and ribavirin (Jain KS, *et. al.,* 2016).

Pyrimidine is a six-membered aromatic ring containing two nitrogen atoms at positions 1 and 3 and four carbon atoms at positions 2, 4, 5, and 6. The chemical formula of pyrimidine is C4H4N2, and its molecular weight is 80.09 g/mol. The ring is planar and exhibits a resonance structure in which the double bonds between positions 2 and 4 and between positions 4 and 6 can move between the two nitrogen atoms as shown in Fig. 1. Pyrimidine can be synthesized using various methods, including the Biginelli reaction, the Borsche-Drechsel cyclization, and the Debus-Radziszewski reaction. The Biginelli reaction involves the condensation of an aldehyde or ketone, a urea, and an acid catalyst in the presence of an alcohol solvent to yield a dihydropyrimidine (Pels Rijcken WR, *et. al.,* 1990). The dihydropyrimidine is then oxidized using mild oxidants such as hydrogen peroxide or potassium permanganate to yield the desired pyrimidine. The Borsche-Drechsel cyclization involves the cyclization of an ethyl 2-amino-4, 6-dimethoxypyrimidine-5-carboxylate using phosphorous oxychloride or thionyl chloride to yield pyrimidine-5-carboxylic acid (Choy N, *et. al.,* 2000). The Debus-Radziszewski reaction involves the condensation of an aldehyde, an amine, and a β-keto ester in the presence of an acid catalyst to yield a dihydropyrimidine, which can be oxidized to yield the desired pyrimidine (Stiernet P, *et. al.,* 2019).



Pyrimidine

Fig. 1: Chemical Structure of Pyrimidine

Pyrimidine analogues are compounds with a chemical structure similar to pyrimidine but with different substituents attached to the ring. These compounds can be classified into two categories: pyrimidine nucleosides and pyrimidine derivatives. Pyrimidine nucleosides are compounds made up of a pyrimidine base linked to a sugar molecule (Chiacchio MA, *et. al.*, 2019). These compounds are the building blocks of DNA and RNA and play a critical role in cellular metabolism. Pyrimidine nucleosides include cytidine, uridine, and thymidine, which are essential for the synthesis of DNA and RNA. Pyrimidine derivatives are compounds that contain a pyrimidine ring with one or more substituents attached to the ring (Lagoja IM. *et. al.*, 2005). These substituents can be either alkyl, aryl, or hetero-aryl groups and can significantly alter the biological activity of the compound. Pyrimidine derivatives include a wide range of compounds, such as anticancer agents, antiviral agents, and antihypertensive agents (Keri RS, *et. al.*, 2015).

Pyrimidine is an aromatic heterocyclic compound similar to pyridine. It is one of the three diazines (unsaturated six-membered rings containing two nitrogen atoms) that has two nitrogen atoms at positions 1 and 3 in the ring (Selvam TP, *et. al.*, 2015). Heterocyclic compounds carrying pyrimidine rings are of enormous importance because they represent a vital family of natural and synthetic products, several of which display valuable clinical applications and bioactivities (ur Rashid H, *et. al.*, 2021).

Substituted pyrimidines and purines are extensively found in living things and are among the leading compounds investigated by chemists. Pyrimidines represent the most abundant members of the diazine class, with thymine, uracil, and cytosine being key components of deoxyribonucleic acid and ribonucleic acid (Grazia Martina M, *et. al.*, 2023). Moreover, the pyrimidine moiety occurs in several natural products, for instance, vitamin B1 (thiamine), and various synthetic products, such as barbituric acid and veronal, which are used as soporific drugs as shown in Fig. 2 and Fig. 3.

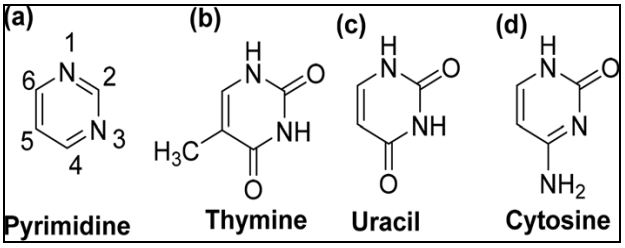


Fig. 2: Chemical structures of pyrimidine, thymine, uracil, and cytosine

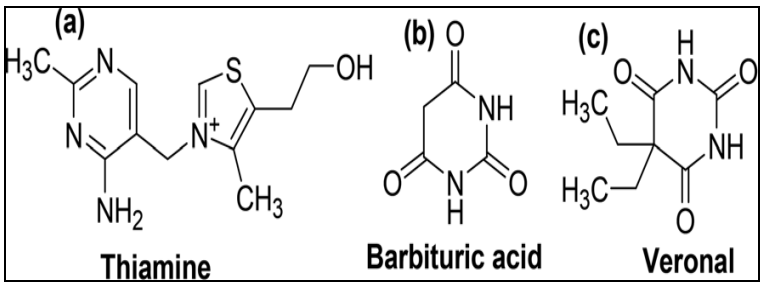


Fig. 3: Chemical structures of thiamine, barbituric acid, and veronal

2. Synthesis of Pyrimidine Analogues:

Pyrimidine analogues can be synthesized using classical or modern methods. Classical methods include the Biginelli, Gewald, Knorr, and Debus-Radziszewski reactions, which involve the condensation of aldehydes, ketones, amines, and carboxylic acids (Gangjee A, *et. al.*, 2004). Modern methods, such as transition-metal-catalysed reactions, click chemistry, and microwave-assisted reactions, are more efficient. Transition-metal-catalysed reactions use transition metal catalysts to form C-C or C-N bonds (Polshettiwar V, *et. al.*, 2008). Click chemistry is a rapid and efficient tool for synthesizing complex molecules, while microwave-assisted reactions utilize microwave radiation to accelerate chemical reactions, resulting in faster reaction times, higher yields, and reduced waste (Pałasz A, *et. al.*, 2015).

The choice of synthetic method depends on the properties of the desired pyrimidine analogue and the goals of the synthesis (Sasada T, *et. al.*, 2009). Some methods of synthesizing pyrimidine analogues are described below:

- **Synthesis via ZnCl2-catalyzed three-component coupling reaction:** This approach involves a three-component coupling reaction comprising substituted enamines, triethyl orthoformate, and ammonium acetate under ZnCl2 catalysis, resulting in the synthesis of numerous 4,5-disubstituted pyrimidine analogues in a single step (Foley DJ, *et. al.*, 2020).

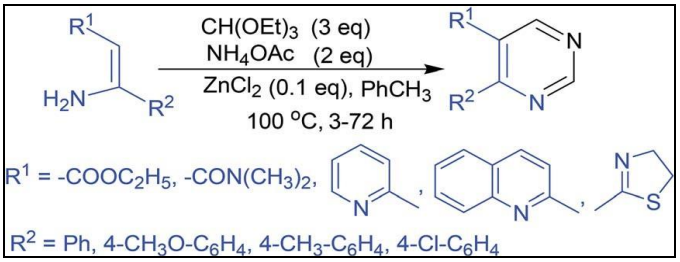


Fig. 4: Synthesis via ZnCl2-catalyzed three-component coupling reaction.

- **Synthesis via K2S2O8-facilitated oxidative annulation reaction:** This approach involves a K2S2O8-facilitated oxidative annulation reaction with formamide as a route towards pyrimidines. Activation of Acetophenone–formamide conjugates resulted in the formation of 4-arylpyrimidines (Jadhav SD, *et. al.*, 2017).

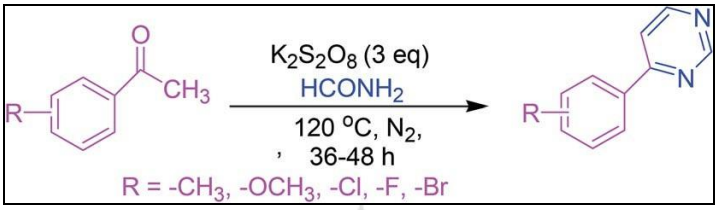


Fig. 5: Synthesis via K2S2O8-facilitated oxidative annulation reaction.

- **Synthesis via Cyclization of ketones with nitriles:** This method involves the synthesis of distinctly substituted pyrimidines through a simple and cost-effective procedure that involves the cyclization of ketones with nitriles under Cu-catalysis in the presence of a base (Su L, *et. al.*, 2018).

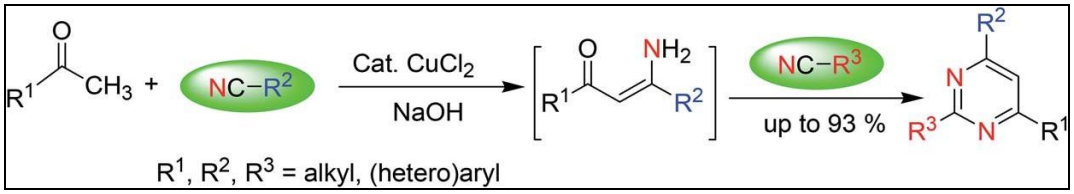


Fig. 6: Synthesis via Cyclization of ketones with nitriles

- **Synthesis via reactions of carbonyl compounds with amidine:** This approach involves the regioselective reaction of carbonyl compounds (esters, aldehydes, and ketones) with amidines in the presence of (2, 2, 6, 6-tetramethylpiperidin-1-yl) oxyl (TEMPO) and an in situ prepared recyclable iron (II)-complex. The reactions progress via a TEMPO complexation/ enamine addition/transient a-occupation/b-TEMPO elimination/cyclization order, resulting in the synthesis of numerous pyrimidine analogs (Chu XQ, *et. al.*, 2017).

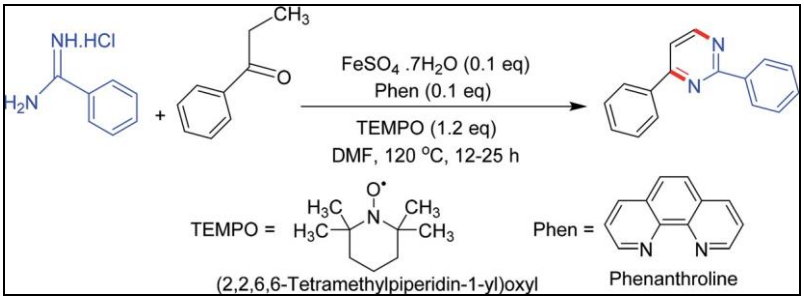


Fig. 7: Synthesis via reactions of carbonyl compounds with amidine

- **Synthesis via base-facilitated intermolecular oxidative C–N bond fabrication:** This method involves a base-facilitated intermolecular oxidative C–N bond fabrication of allylic C(sp3)–H and vinylic C(sp2)–H of allylic compounds with amidines to allow easy synthesis of pyrimidines. This approach results in the synthesis of polysubstituted pyrimidines under oxygen as a solitary oxidant, ensuring the supply of protective group-free nitrogen, high efficiency, worthy functional group leniency, and environmental sustainability (Guo W, *et. al.*, 2016).

Fig. 8: Synthesis via base-facilitated intermolecular oxidative C–N bond fabrication

- **Synthesis via 4-HO-TEMPO-mediated [3 + 3] annulation of amidines with saturated ketones under Cu-catalysis:** An effective and smooth synthesis of functionally vital pyrimidines has been reported by 4-HO-TEMPO-facilitated [3 + 3] annulation of commercial-grade amidines with saturated ketones under Cu-catalysis. This method provides a new protocol for the synthesis of pyrimidine derivatives via a cascade reaction of oxidative dehydrogenation/annulation/oxidative aromatization using direct beta-C(sp3)-H functionalization of saturated ketones succeeded by annulation with amidines (Zhan JL., *et. al.*, 2016).

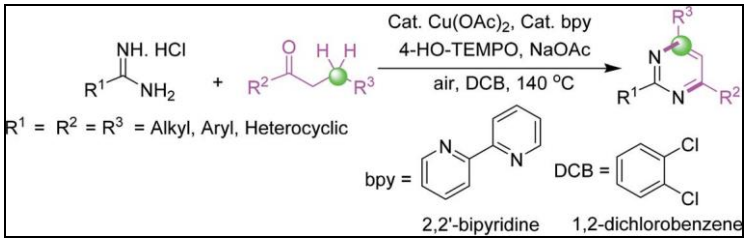


Fig. 9: Synthesis via 4-HO-TEMPO-mediated [3 + 3] annulation of amidines with saturated ketones under Cu-catalysis

- **Synthesis via Viable multicomponent synthesis:** Pyrimidines are also obtained from amidines and up to three (dissimilar) alcohols under iridium-catalysis through a regio-selective, multicomponent synthetic approach. The reaction involves a series of condensation and dehydrogenation phases that produce a particular C-C and C-N bond configuration. Deoxygenating of the alcohols is accomplished through condensation, whereas aromatization is achieved via dehydrogenations. This sustainable multicomponent synthesis is catalyzed by PN5P-Ir-pincer complexes with high efficiency (Deibl N, *et. al.*, 2015).

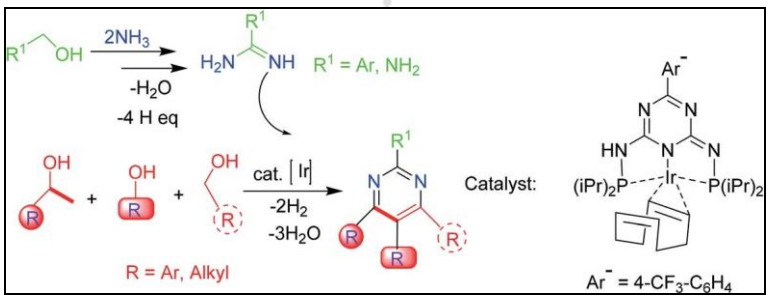


Fig. 10: Synthesis via Viable multicomponent synthesis

- **Synthesis of 2-substituted pyrimidine-5-carboxylic ester:** A simple and convenient method for the synthesis of several 2-substituted pyrimidine-5-carboxylic esters has been reported. In this approach, the sodium salt of 3,3-dimethoxy-2-methoxycarbonylpropen-1-ol is treated with various amidinium salts to produce the target compounds (Zhichkin P, *et. al.*, 2002).

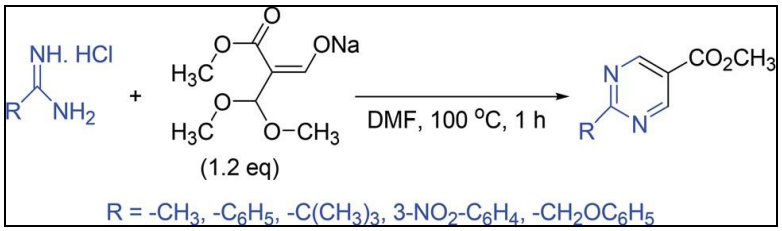


Fig. 11: Synthesis of 2-substituted pyrimidine-5-carboxylic ester

- **Synthesis of densely substituted pyrimidines:** Synthesis of C4-heteroatom derivatized pyrimidines is accomplished by condensation of cyanic acid analogues with N-vinyl/aryl amides. In this reaction, the utilization of cyanic bromide and thiocyanatomethane offers flexible azaheterocycles poised for additional substitution (Ahmad OK, *et. al.*, 2009) and (Gayon E, *et. al.*, 2012).

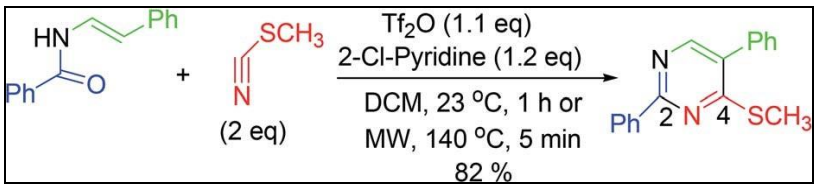


Fig. 12: Synthesis of densely substituted pyrimidines

- **Synthesis via stereo selective access to beta-enaminones under NaOH catalysis:** This strategy consists of a rearrangement of propargylic hydroxylamines under NaOH catalysis, which permits efficient and stereo selective access to Cbz-protected beta-enaminones. Subsequent preparation of pyrimidines displays the synthetic application of these beta-enaminones (Gao F, *et. al.*, 2019).

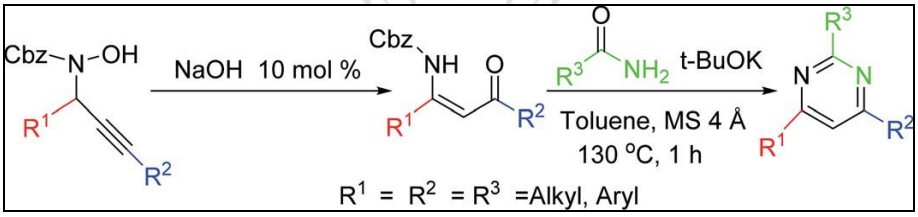


Fig. 13: Synthesis via stereo selective access to beta-enaminones under NaOH catalysis

3. Structure Activity Relationship (SAR) of Pyrimidine:

Pyrimidine analogue SAR studies investigate the link between chemical structure and biological activity (Xiao J, *et. al.*, 2011). Pyrimidine ring modifications can also affect pharmacokinetic properties, such as solubility, permeability, and metabolic stability. Medicinal chemists use SAR to design and synthesize pyrimidine analogues with improved properties, including potency, selectivity, and pharmacokinetics, for use as pharmaceuticals (Zhang Y, *et. al.*, 2017).

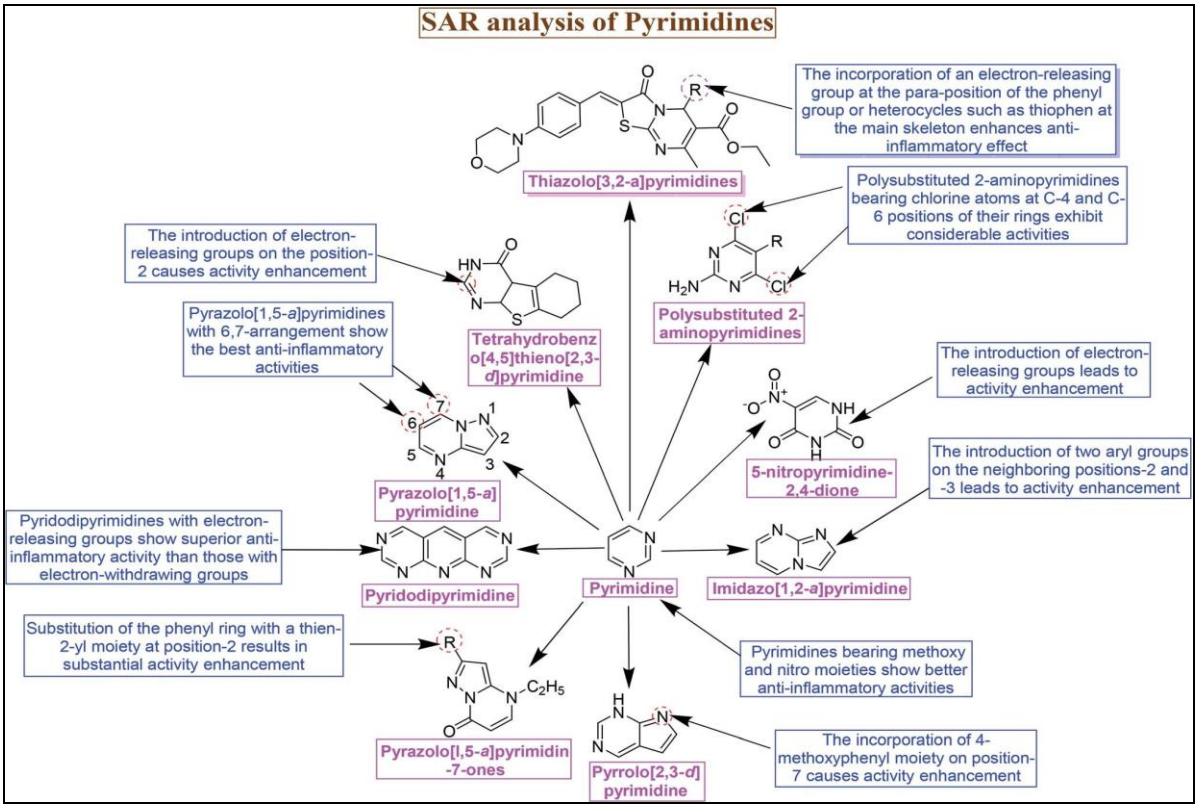


Fig. 14: Structure Activity Relationship (SAR) analysis of Pyrimidines

Here are some possible substitutions which can be done to alter the activities of pyrimidine such as solubility, permeability, and metabolic stability:

- The introduction of electron-releasing moieties at position-2 of the core pyrimidine in tetrahydrobenzo [4,5] thieno [2,3-d] pyrimidine causes activity enhancement (Fatahala SS, *et. al.*, 2017).

- The incorporation of a 4-methoxyphenyl moiety at position-7 of pyrrolo[2,3-d]pyrimidine results in activity enhancement (Abdelgawad MA, *et. al.*, 2018).

- Pyridodipyrimidine derivatives with electron-releasing moieties show superior anti-inflammatory potential compared to derivatives of the same type with electron-withdrawing moieties (Raffa D, *et. al.*, 2009).

- Both monoaryl- and bisaryl-substituted 2-amino-pyrimidines exhibit improved activities regardless of the length of the C-5 substituents in polysubstituted pyrimidines (Chang C, *et. al.*, 2021).

- The introduction of two aryl moieties at neighbouring positions-2 and -3 in imidazo [1,2-a]pyrimidines leads to activity enhancement (ur Rashid H, *et. al.*, 2021).

- The presence of a five-membered thiophene moiety at positions-4,6 and an electron-releasing chlorine atom at position-2 of tricyclic pyrimidines improve the anti-inflammatory potential of the target derivatives (Bruni F, *et. al.*, 1993).

- Substitution of the phenyl ring with a thien-2-yl moiety at position-2 in pyrazolo [1,5-a] pyrimidin-7-ones results in substantial activity enhancement (Nofal ZM, *et. al.*, 2011).

- The introduction of 3-chlorophenyl and carboxamide groups at positions-1 and -4 of the pyrazolone ring, respectively, causes substantial enhancement in anti-inflammatory activities of pyrazolediazenyl pyrimidines (Bakr RB, *et. al.*, 2016).

- Pyrimidines bearing a pyrazolyl group in a hybrid configuration with the pyrazolo [3,4-d] pyrimidine moiety exhibit significant anti-inflammatory activities (Almansa C, *et. al.*, 2001).

- Pyrazolo [1, 5-a]pyrimidines with a 6,7-arrangement show the best anti-inflammatory activities (Amr AE, *et. al.*, 2017).

- Pyrimidines containing cycloheptenes fused to their rings display better activities than derivatives containing cyclohexenes fused to their rings (Zarghi A, *et. al.*, 2011).

- The introduction of p-sulfonamide or p-methylsulfone on one of the two aromatic rings in diarylheterocycle encompassing pyrimidines contributes to activity enhancement (Reddy DS, *et. al.*, 2021).

4. Pharmaceutical Applications:

Pyrimidine analogues have found extensive applications in the field of pharmaceuticals due to their broad range of biological activities, making them promising candidates for drug discovery and development (Andrei G, *et. al.*, 2012).

Some of the pharmaceutical applications of pyrimidine analogue is depicted in Fig. 5 and include:

- **Anticancer agents:**

Pyrimidine analogues such as 5-fluorouracil, cytarabine, and gemcitabine are commonly used as chemotherapy drugs due to their ability to inhibit DNA synthesis and cell proliferation, making them effective against a variety of cancers (Laev SS, *et. al.*, 2015).

- **Antiviral agents**:

Pyrimidine analogues like acyclovir and valacyclovir are used as antiviral agents due to their ability to inhibit DNA polymerase, making them effective against viral infections such as herpes and varicella-zoster (Singh K, *et. al.*, 2009).

- **Anti-inflammatory agents:**

Pyrimidine analogues such as leflunomide and teriflunomide have been developed as anti-inflammatory drugs, as they inhibit the production of pro-inflammatory cytokines and leukotrienes (Capasso C., *et. al.*, 2014).

- **Antihypertensive agents:**

Pyrimidine analogues like amlodipine and nifedipine are calcium channel blockers used as antihypertensive agents, as they relax blood vessels and lower blood pressure (Matos LH, *et. al.*, 2018).

- **Antimicrobial agents:**

Pyrimidine analogues such as trimethoprim and sulfamethoxazole are used as antimicrobial agents due to their ability to inhibit bacterial dihydrofolate reductase, an enzyme essential for the synthesis of folic acid (Hawser S, *et. al.*, 2006).

CONCLUSION:

In conclusion, pyrimidine and its analogous are important heterocyclic compounds with various applications in chemistry and pharmacy. Pyrimidine is a fundamental building block of DNA and RNA and plays a critical role in cellular metabolism. Pyrimidine derivatives and analogous have been found to exhibit diverse biological activities, including antiviral, antibacterial, anticancer, and anti-inflammatory properties. The synthesis of pyrimidine can be achieved using various classical and modern methods. Pyrimidine analogous can be classified into pyrimidine nucleosides and pyrimidine derivatives, with the latter having

different substituents attached to the ring, which can significantly alter their biological activity. The significance of substituted pyrimidines and purines in living organisms makes them extensively studied by chemists. The development of pyrimidine-based drugs has led to the discovery of many important pharmaceuticals, including anticancer agents and antiviral drugs. Overall, the importance of pyrimidine and its analogous in various fields underscores the need for continued research in this area.

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