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SYNTHESIS AND PROPERTIES OF AZOMETHINE DERIVATIVES OF 2-AMINO-4,6-DIHYDROXYPYRIMIDINE (A COMPREHENSIVE REVIEW)

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Abstract. 2-Amino-4,6-dihydroxypyrimidine (CAS 56-09-7) represents an indispensable heterocyclic building block widely exploited in organic synthesis, agrochemicals and pharmaceutical design. Although the baseline molecule features modest direct biological efficacy due to its highly stable, neutral tautomeric states, its unique spatial arrangement of three strong electron-donating groups unlocks exceptional reactivity. This review systematically maps the core chemical and physical properties of the molecule, addresses its dynamic keto-enol (lactam-lactim) structural isomerism, classifies its nucleophilic and electrophilic reaction centers and details the vast spectrum of biological activities—including antiviral, anticancer, anti-inflammatory and antimicrobial profiles – unlocked upon derivative functionalization.

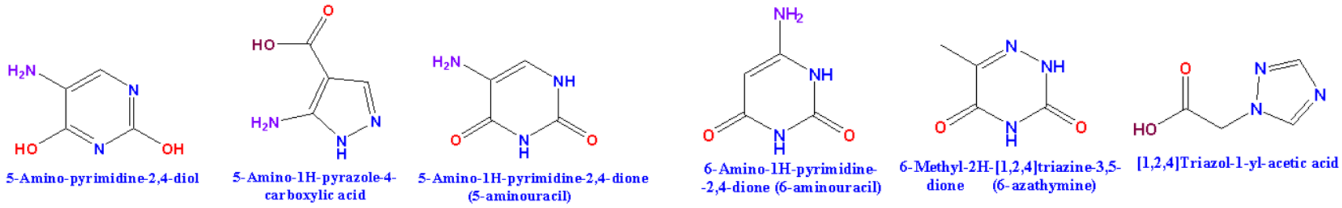
Keywords: Pyrimidine intermediate, tautomerism, electrophilic substitution, privileged scaffold.

Introduction. The pyrimidine heterocycle is an elemental structural motif found throughout natural nucleic acids and premium synthetic drugs [1]. Among its multi-substituted derivatives, 2-amino-4,6-dihydroxypyrimidine (2-ADHP) serves as a key industrial precursor and valuable heterocyclic scaffold widely utilized as a key intermediate in the synthesis of pharmaceuticals, biochemical research agents, and sulfonylurea herbicides. Due to the coexistence of a highly nucleophilic primary amine, electrophilic/nucleophilic pyrimidine ring carbons, and tautomeric hydroxyl groups (which exist in equilibrium with their keto/amide forms), the molecule exhibits diverse reactivity with its 4 types of reaction centers [2].

Physical Properties. 2-aminopyrimidine-4,6-diol isolates as a white to light-yellow crystalline powder with an extraordinarily high melting point exceeding 300 °C, at which it undergoes thermal decomposition. Due to strong intermolecular network stacking, it exhibits minimal solubility in neutral organic solvents and cold water, but readily dissolves in aqueous alkaline solutions through stable salt formation [3]. Its predicted acidity constant (pKa) rests near 7.45 [4].

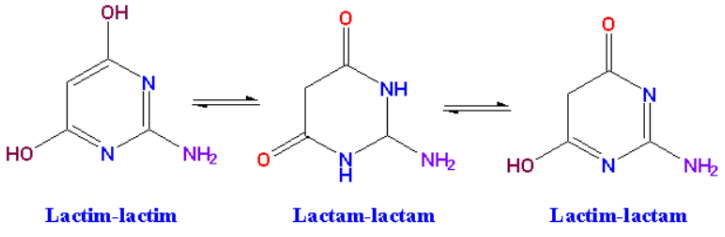
When discussing the isomers of 2-amino-4,6-dihydroxypyrimidine, they are classified into two categories: *I. Constitutional (structural) isomers*– compounds with the same molecular formula $C_4H_5N_3O_2$ but different atom connectivities. Several structural isomers (close to sixteen)[5] share the exact same chemical formula but possess different functional groupings or core rings (several examples are illustrated in fig.1): *4-Amino-2,6-dihydroxypyrimidine:* An isomer where the amino group resides at the 4-position instead of the 2-position; *5-Amino-1H-4-pyrazole-4-carboxylic acid:* a structural ring isomer where the six-membered pyrimidine ring is swapped for a five-membered pyrazole ring adorned with a carboxylic acid functional group; *5-Amino-2,4-dihydroxypyrimidine (5-Aminouracil):* A biologically critical isomer where the amino group is attached at the 5-position.

Figure 1. Structural isomers of 2-ADHP



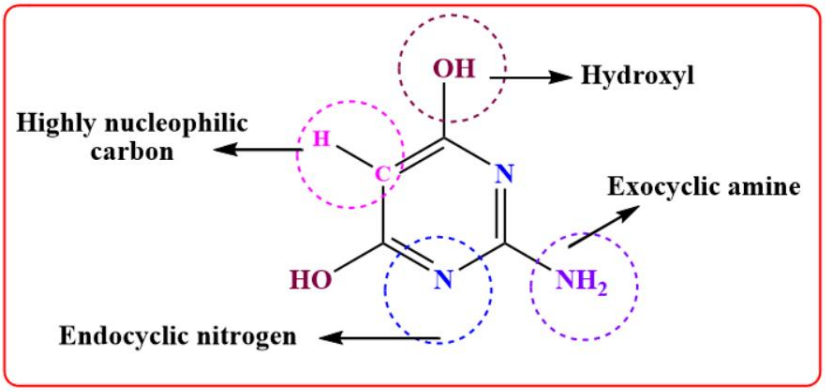
II. *Tautomers* (dynamic, interconverting isomers) – that exist in equilibrium (fig.2). A critical parameter in managing this molecule's reactivity is its **lactam-lactim (keto-enol) tautomerism** [6]. The theoretical *dihydroxy* (dilactim) form is not the absolute state of the molecule under environmental conditions. High-resolution IR and solid-state NMR studies confirm that in the crystalline phase, the molecule heavily prefers the *dioxo (dilactam) form* (2-aminopyrimidine-4,6(1H,3H)-dione). This preference is driven by the thermodynamic stability of formatting highly packed, cooperative sheets of intermolecular hydrogen bonds. In polar aprotic solvents such as DMSO, spectroscopic analyses reveal a dynamic equilibrium dominated by the *mono-oxo mono-hydroxy (lactam-lactim) form* (2-amino-6-hydroxy-4(1H)-pyrimidinone) [3].

Figure 2: Tautomeric isomers of 2-ADHP



Mapping of Reaction Centers. The electronic effects of three strong electron-donating groups (one amino and two hydroxyl) render this pyrimidine ring unique: it simultaneously displays the characteristics of an electron-overrich aromatic substrate and a reactive heterocycle. The presence of three heteroatom groups on a single six-membered ring induces a highly polarized electron distribution, providing four isolated chemical reaction centers:

Figure 3. Classification of reaction centers in the 2-ADHP molecule.



1. Nucleophilic Groups (Electron Donors): ***The 2-Amino Group (-NH₂):*** Located between both ring nitrogen atoms, it exerts a powerful positive mesomeric effect (+M), pushing electron density into the conjugated system. Target reactions: *Deactivation by Cross-Conjugation:* Unlike aliphatic amines, its lone pair is heavily delocalized into the pyrimidine ring [7]. It participates in condensation reactions (e.g., with aldehydes to form Schiff bases) or acylation, but requires harsher conditions than ordinary amines [7]. ***The 4- and 6-Oxygen Atoms*** (-OH or =O): Act as strong resonance donors in the enol form and function as potent hydrogen-bond acceptors or coordination sites in the keto form [8]. ***The C5 carbon*** acts as a highly reactive, electron-rich nucleophilic center due to the positive mesomeric effect (+M) from neighboring oxygen and nitrogen groups [9]. This significant electron density allows the C5 position to readily participate in electrophilic substitution reactions, such as nitrosation and halogenation, making it a key site for heterocyclic synthesis [2, 9]. And also this molecule is an exceptional substrate for the synthesis of purines (such as guanine alternatives), pteridines, and complex pharmaceutical frameworks via multicomponent cascade reactions [2]. ***Nitrogens N1 and N3:*** In the traditional pyrimidine ring, the nitrogen atoms typically possess an accessible lone pair in an sp^2 orbital, acting as nucleophilic centers or weak bases. However, in 2-ADHP, the electronic nature of the N1 and N3 positions is fundamentally altered due to intense tautomeric keto-enol stabilization [8]. *Amide-like Character (Imide System):* In the predominant dioxo-tautomeric form, the lone pairs of both N1 and N3 are heavily delocalized into the adjacent carbonyl groups (C4=O and C6=O). This strong resonance conjugation effectively deactivates their nucleophilicity under neutral conditions. Instead of acting as Lewis bases, these positions function as secondary cyclic amides (lactams) [9]. *Distinct N–H Acidity:* Because the nitrogen lone pairs are pulled into the carbonyl π-systems, the hydrogen atoms attached to N1 and N3 become remarkably acidic

compared to standard heterocycles [9]. Under basic conditions, these N–H protons are easily abstracted, generating a highly resonance-stabilized pyrimidine anion.

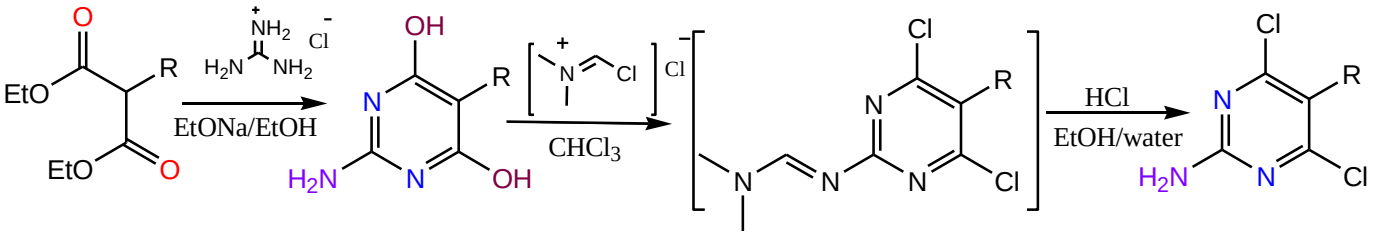
Ambident Nucleophilicity via Deprotonation: Once deprotonated, the resulting negative charge is shared between the N1/N3 nitrogens and the O4/O6 oxygens. This transforms the N1 and N3 sites into active nucleophilic centers capable of selective *regioselective N-alkylation or glycosylation* [10]. This specific reactivity is a cornerstone in the synthetic pathways directed toward modified nucleosides and antiviral purine analogues [10].

2. Electrophilic Groups (Electron Acceptors). Carbonyl Carbons (C4 and C6): In the dioxo-tautomer, these positions are electron-deficient due to the strong inductive (-I) and mesomeric (-M) effects of the carbonyl oxygens, making them susceptible to nucleophilic attacks under specific conditions [7].

Synthesis and Chemical Transformations of 2-Amino-4,6-Dihydroxypyrimidine.

According to the protocols established by Jansa et al., the synthesis of 5-substituted 2-amino-4,6-dichloropyrimidines requires an in situ protection strategy due to the structural interference of the C-2 amino group [2]. At first, synthesis of 2-amino-4,6-dihydroxypyrimidines (Scheme 1) via base-catalyzed condensation of substituted malonic diesters with guanidine [11,12,13] was optimized for multi-gram scales. Using methanol or ethanol ensured high conversion, while post-reaction dilution with water and neutralization with acetic acid facilitated quantitative precipitation and isolation with high purity [2]. The bis-deoxohalogenation of 5-substituted 2-amino-4,6-dihydroxypyrimidines was using a modified Vilsmeier–Haack–Arnold reagent [14] system consisting of $POCl_3$ and achieved DMF under reflux conditions at 95–105°C, 4 hours. This sequence temporarily converts the exocyclic amine into a dimethylformamidine protecting group while replacing the lactam oxygens with chlorine atoms. Subsequent acid-catalyzed ice-water hydrolysis selectively cleaves the formamidine group, converting it back into a primary amine (-NH_2) (Scheme 1). The solution is carefully neutralized using a cold alkaline solution (such as aqueous NaOH or $NaHCO_3$) until the pH reaches approximately 6–7. This causes the target 5-substituted 2-amino-4,6-dichloropyrimidine to precipitate out as a solid, which is then filtered, washed with water-ethanol mixture, and dried under high vacuum [2].

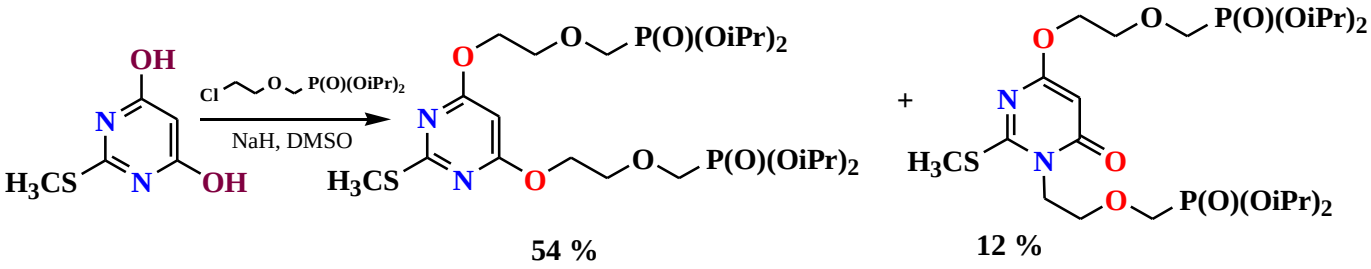
Scheme 1. General synthesis of 5-substituted 2-amino-4,6-dihydroxypyrimidines and 2-amino-4,6-dichloropyrimidines



According to Dolakova et al. (2009), the efficient synthesis of 4,6-bis[(phosphonomethoxy)alkoxy]pyrimidines requires regioselective O-alkylation of 2-

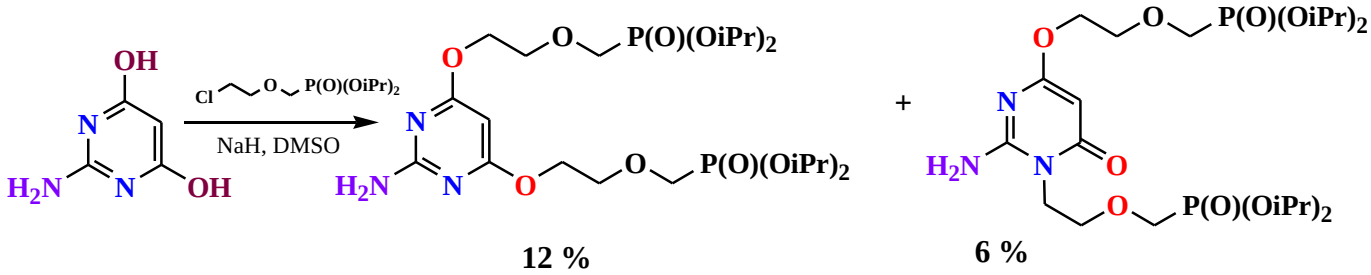
(methylsulfanyl)pyrimidine-4,6-diol using sodium hydride or cesium carbonate in anhydrous DMSO at 60–80 °C (Scheme 2). This optimized method drives double alkylation at the C-4 and C-6 positions, avoiding the poor yields associated with direct nucleophilic aromatic substitution, with the choice of solvent being critical for high conversion [15]. Particularly, in scheme 2 shown the products with satisfactory yields: *O*–alkylated regioisomer 54%; *N*–alkylated regioisomer was formed in 12% yield [15].

Scheme 2. Regioselective O-alkylation of 2-(methylsulfanyl)pyrimidine-4,6-diol



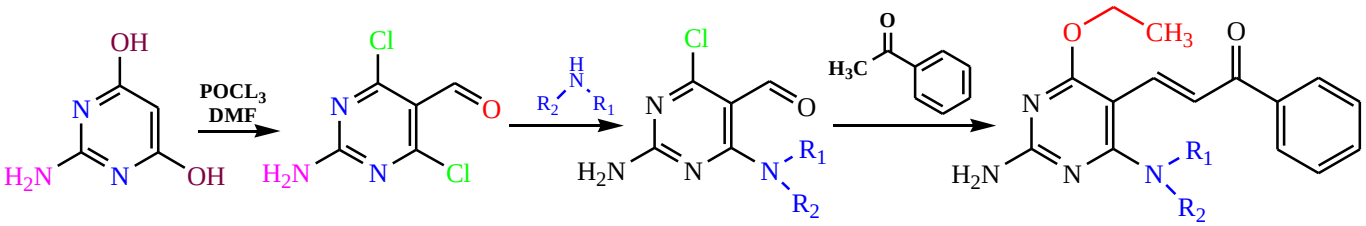
Alkylation of 2-amino-4,6-dihydroxypyrimidine with 2-(diisopropoxyphosphorylmethoxy) ethylchloride (Scheme 3) gave a mixture of disubstituted regioisomers with 18 % yield (**2:1** ratio accordingly) and O-alkylated product 2-amino-4,6-bis[2-(phosphonomethoxy) ethoxy]pyrimidine was reported to show antiretroviral activity [16].

Scheme 3. Alkylation of 2-amino-4,6-dihydroxypyrimidine



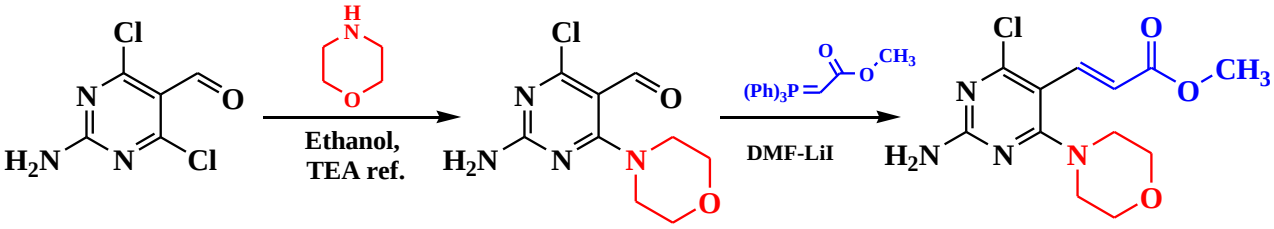
The 5-formyl group on 2-amino-4,6-dichloropyrimidine-5-carbaldehyde activates the C-4 and C-6 positions for nucleophilic aromatic substitution, allowing regioselective mono-amination at room temperature in solvents like THF or acetonitrile [17]. Utilizing triethylamine as a base, the reaction efficiently yields 2,4-diamino-6-chloropyrimidine-5-carbaldehyde derivatives within 1–3 hours [17]. The reaction of 2-amino-4,6-dichloropyrimidine-5-carbaldehyde with acetophenone under basic, protic conditions (NaOH/ethanol) [18] involves a Claisen–Schmidt condensation at the C-5 formyl group followed by tandem nucleophilic aromatic substitution (S_NAr) and solvolysis at the C-4/C-6 positions (Scheme 4). The process generates heavily functionalized mixed alkoxy-chalcone networks, with the strong base driving both condensation and collateral substitution chemistry, as detailed by Trilleras et al. (2022). The synthesis of the key intermediate, 2-amino-4,6-dichloropyrimidine-5-carbaldehyde, was achieved starting from 2-amino-4,6-dihydroxypyrimidine via a classic Vilsmeier–Haack formilation method [19].

Scheme 4. Claisen–Schmidt condensation



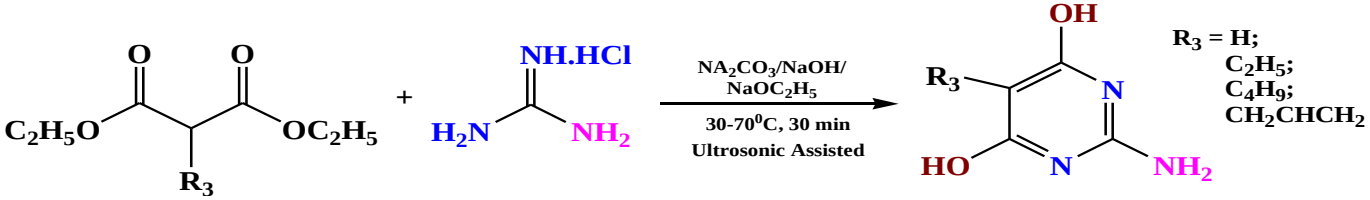
The synthesis of methyl (*E*)-3-(2-amino-4-chloro-6-morpholinopyrimidin-5-yl)acrylate (Scheme 5) is achieved via a base-free Schlosser-modified Wittig olefination of 2-amino-4-chloro-6-morpholinopyrimidine-5-carbaldehyde (synthesized from 2-amino-4,6-dichloropyrimidine-5-carbaldehyde [20], yielding 80% [21]. This method utilizes methyl (triphenylphosphoranylidene)acetate in DMF to produce the specific (*E*)-isomer with exclusive stereochemical control [21].

Scheme 5. Amination via the S_NAr mechanism and Wittig olefination



The construction of the 2-aminopyrimidine core is widely achieved through a classical [3+3] cyclocondensation strategy. In this bimolecular assembly, guanidine or its derivative serves as the trinucleophilic component, while β-dicarbonyl compounds or their reactive analogs (β-ketoesters, β-ketonitriles, and acid chlorides) function as the dielectrophilic partners [22]. The work of Bayramo˘glu et al. accomplished the synthesis of 2-ADHP and its 5-alkyl or 5-alkylidene derivatives with much stronger condensing agent sodium ethoxide ($NaOC_2H_5$), to achieve effective cyclization. They used ultrasound-assisted method and reaction was carried out at a temperature of 60–70 °C for 30 min (Scheme 6). To drive the cyclization of simpler variants, such as 2-amino-4,6-dimethylpyrimidine and 2-amino-4-hydroxy-6-methylpyrimidine Weak inorganic bases like sodium carbonate (Na_2CO_3) or sodium hydroxide (NaOH) possess sufficient reactivity (100 °C, 5-8 hours, yields 54% and 78%) [23].

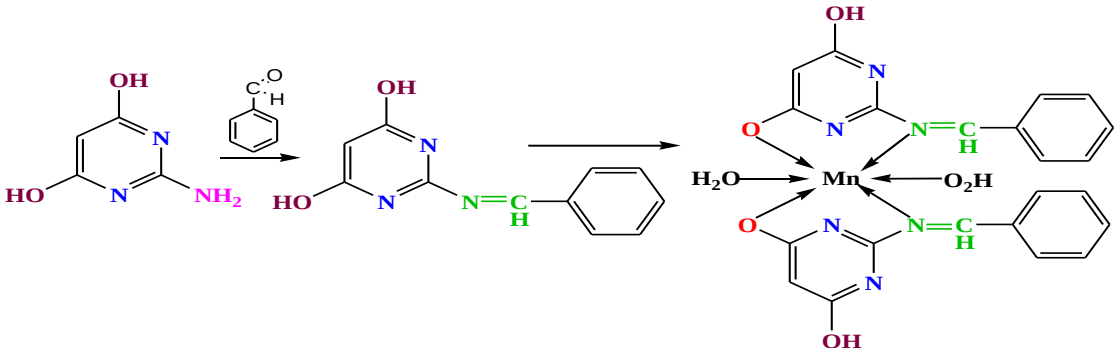
Scheme 6. Synthesis of 2-aminopyrimidine using β-dicarbonyl compounds and guanidine



According to studies DT Sakhare (researcher from India) The Schiff base ligand (L) – synthesized (Scheme 7) via condensation of 2-ADHP and benzaldehyde 1:1 molar ratio (modification methods of [24]). Reagents refluxed in 50 ml of dry ethanol for 4 hours (yield 70%) [25]. Mn(II) complexes are subsequently prepared by mixing 2 moles of the ligand (L) with 1 mole of manganese nitrate, adjusting the pH to 7–8 with 10% alcoholic ammonia, and

refluxing in ethanol for 3 hours, then filtered and dryed. Finally, octahedral Mn(II) complex $[Mn(L)_2(NO_3)_2]$ was obtained with 60% yield. The complex display enhanced antimicrobial properties against both Gram-negative and Gram-positive bacteria [25].

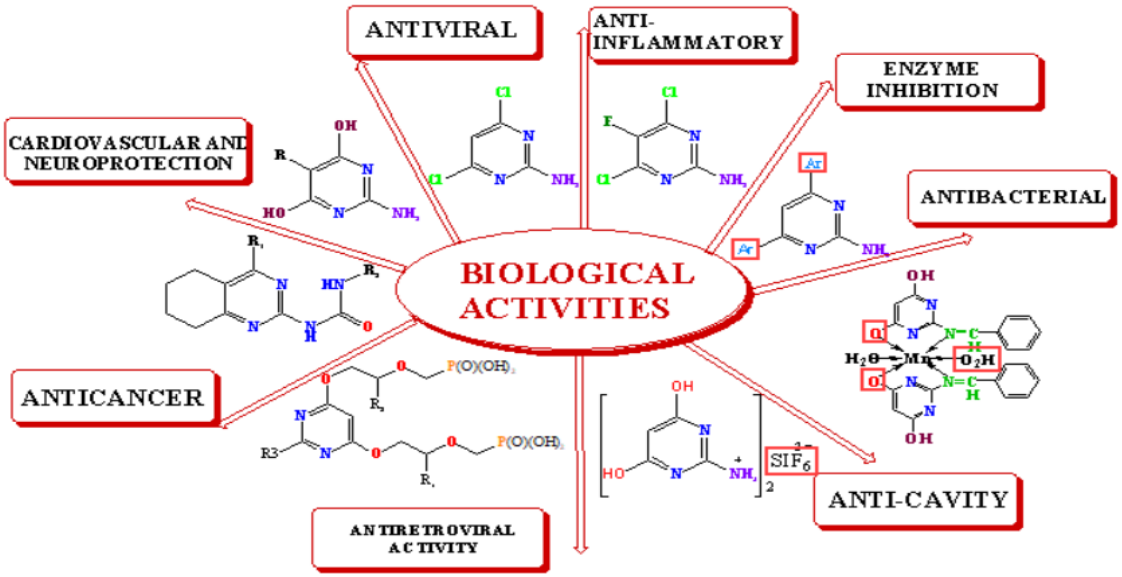
Scheme 7. Mn (II) complex of biologically active bidentate ligand



The Biological Prominence of 2-Amino-4,6-dihydroxypyrimidine Scaffolds.

In the fields of medicinal chemistry and drug discovery, heterocyclic rings serve as the fundamental building blocks for designing new therapeutic agents. Among these structures, the pyrimidine ring is exceptionally important because it forms the core of natural nucleic acids, such as cytosine, thymine, and uracil. Because pyrimidine structures are naturally present in living organisms, synthetic pyrimidine derivatives are highly valued for their ability to interact easily with biological targets, enzymes, and cellular receptors. Among these derivatives, 2-amino-4,6-dihydroxypyrimidine has emerged as a unique and highly versatile molecular scaffold. By itself, the unmodified 2-amino-4,6-dihydroxypyrimidine molecule exhibits minimal direct pharmacological or biological activity. However, derivatives (fig.4.) built from this core scaffold have demonstrated an incredibly diverse spectrum of applications.

Figure 4. Biological Activities Core Derivatives



➢ Antiviral Activity via Halogenation – replacing the hydroxyl groups (C-4 and C-6) with chlorine using phosphoryl chloride (POC_3) produces 2-amino-4,6-dichloropyrimidine. The introduction of these electron-withdrawing chlorine atoms increases the reactivity of the pyrimidine core. This modification allows the molecule to act as an inhibitor of viral morphogenesis, disrupting viral capsid assembly by preventing the cleavage of structural precursors, particularly in RNA viruses such as poliovirus [2, 26].

➢ Anti-Inflammatory Effects via C-5 Modification – introducing highly electronegative groups, such as fluorine, at the C-5 position of the pyrimidine core enables the synthesis of compounds like 5-fluoro-2-amino-4,6-dichloropyrimidine. This structural modification alters the electronic properties of the molecule, significantly suppressing immune-activated nitric oxide (NO) production in immune cells. Specifically, this derivative exhibits potent anti-inflammatory activity with an IC_{50} value of 2μM, effectively preventing the overproduction of hazardous NO during inflammatory responses [2, 27].

➢ Antibacterial Activity via Schiff Base Formation – condensation of the C-2 amino group of 2-ADHP with aromatic aldehydes (such as benzaldehyde or 2-hydroxy-1-naphthaldehyde) yields azomethine-containing heterocyclic Schiff base ligands. This ligands coordinated with divalent transition metal ions like Mn(II) or Cu(II), exhibit potent antibacterial activity against both Gram-positive (e.g., *Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative (e.g., *Escherichia coli*) pathogens by disrupting bacterial cell wall synthesis and metabolic processes [24, 25].

➢ Enzyme Inhibition in Diabetes Management – Introducing aromatic rings at the C-4 and C-6 positions of the pyrimidine core via cross-coupling reactions yields various 2-amino-4,6-diarylpyrimidines. The bulky hydrophobic diaryl architectures establish strong binding interactions within the active pockets of α-glucosidase and α-amylase. This precise structural fit competitively suppresses these key enzymes, preventing the breakdown of complex carbohydrates into glucose and offering a potent therapeutic strategy for managing Type 2 diabetes. [28].

➢ Anticancer Properties via Bicyclic Fusion – Fusing the C-5 and C-6 positions of the pyrimidine core into a rigid, two-ring system creates a bicyclic scaffold (such as thieno- or furopyrimidine) that acts as an ATP-competitive pharmacophore. This structural arrangement positions the molecule precisely within the hinge region of the Vascular Endothelial Growth Factor Receptor-2 (VEGFR-2) kinase. By blocking this specific receptor pathway, the compound effectively suppresses neovascularization to cut off the tumor blood supply (anti-angiogenesis) and subsequently triggers programmed cancer cell death via apoptosi [29].

➢ Antiretroviral activity. Direct alkylation of 2-ADHP yields the O-alkylated product 2-amino-4,6-bis[2-(phosphonomethoxy)ethoxy]pyrimidine, demonstrating significant inhibition against human immunodeficiency virus type 1 (HIV-1), HIV-2, and Moloney murine sarcoma virus (MSV) by acting as an alternative substrate that triggers viral DNA chain termination. [16].

➢ Cardiovascular and Neuroprotection – Incorporating lipophilic alkyl chains (such as butyl or pentyl) at the C-5 position of 2-aminopyrimidine-4,6-diols significantly enhances their membrane permeability and blood-brain barrier penetration. These structural modifications allow the molecules to act as selective adenosine receptor agonists. By activating adenosine signaling pathways, these derivatives regulate essential downstream cellular enzymes, effectively safeguarding cerebral and myocardial tissues against ischemic injuries and programmed cell death caused by hypoxia [30].

➢ Dental Biomaterials and Anticaries Effects – reacting the pyrimidine core with hexafluorosilicic acid (H_2SiF_6) yields a stable crystalline salt, 2-amino-4,6-dihydroxypyrimidinium hexafluorosilicate. Within the oral cavity, the organic pyrimidinium cation restricts the growth and metabolic activity of cariogenic pathogens, such as Streptococcus mutans. Concurrently, the sustained release of fluoride and silicate ions synergistically promotes the remineralization of dental enamel, significantly enhancing its structural resistance against acid-induced erosion. [31, 32].

CONCLUSION. 2-amino-4,6-dihydroxypyrimidine serves as an exceptionally versatile molecular scaffold in modern medicinal and industrial chemistry. While the unmodified base molecule shows little independent biological action, its unique layout—featuring highly customizable reactive sites at the C-2, C-5, and C-4/C-6 positions—makes it an ideal starting point for building complex drugs. As demonstrated by these ten examples, minor adjustments to the core ring can completely shift the chemical properties of the molecule. These changes allow researchers to create highly targeted therapies ranging from powerful antivirals and selective anticancer agents to effective agricultural tools and advanced dental biomaterials. Ultimately, the structure-activity relationships outlined in this review highlight how important this single pyrimidine core remains for discovering new, functional molecules across multiple scientific fields.

2-Amino-4,6-dihydroxypyrimidine bridges basic electronic structure principles with high-utility drug architecture. Its multi-dentate tautomeric nature, combined with highly separated electrophilic and nucleophilic target sites, secures its rank as a **"privileged scaffold."** Our future research directions will likely emphasize its role in automated sustainable green synthesis (e.g., microwave-assisted multicomponent reactions) and the creation of targeted covalent inhibitors (TCIs) aimed at defeating drug-resistant oncology targets.

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