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Thiazole as a Privileged Scaffold in Drug Design: A Review

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Abstract: ***Thiazole, a five-membered heteroaromatic ring comprising nitrogen and sulfur atoms, has emerged as a privileged scaffold in medicinal chemistry due to its ability to interact with a wide range of biological targets. Its aromaticity, electronic versatility and ease of functionalization make it a valuable structural unit in the design of pharmacologically active molecules. Thiazole-based compounds exhibit favourable physicochemical and pharmacokinetic properties, which contribute to their role in numerous clinically approved drugs and investigational agents.***

This review highlights the structural features, synthetic methodologies and diverse biological activities of thiazole and its derivatives. Classical and modern synthetic routes, including green and metal-catalyzed protocols, are discussed along with structure–activity relationship (SAR) insights. A broad range of pharmacological effects—such as antimicrobial, anticancer, antiviral, anti-inflammatory and antioxidant properties—are analyzed with examples from current research and marketed drugs like ritonavir, pramipexole and meloxicam. Molecular docking and computational studies further underscore thiazole's utility in rational drug design. Future directions emphasize improving selectivity, minimizing toxicity and leveraging AI-based strategies for next-generation drug development.

Key Words: Thiazole, privileged scaffold, heterocyclic compounds, pharmacological activity

Introduction: Heterocyclic compounds are central to modern drug discovery, with nearly 75% of FDA-approved small-molecule drugs containing at least one heterocyclic ring[1]. Among these privileged scaffolds, structural frameworks capable of high-affinity interactions with diverse biological targets have proven especially valuable. Thiazole (fig 1.1), a five-membered aromatic heterocycle containing both nitrogen and sulfur atoms. It is one such scaffold, naturally occurring in thiamine (vitamin B1, fig 1.2) and widely employed in synthetic drug design.

Fig 1.1 Thiazole

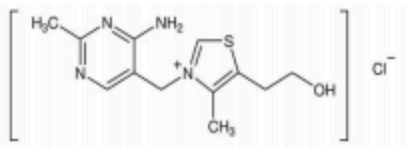

Fig 1.2 Thiamine (Vitamin B1)

Thiazole derivatives display a broad spectrum of pharmacological activities, including antioxidant, antibacterial, antifungal, anticancer, antiallergic, antihypertensive, anti-inflammatory, antimalarial and antipsychotic effects[2-4]. Their aromaticity and electron-rich nature facilitate strong interactions with biological targets, enhancing drug-likeness and pharmacokinetics. More than 18 FDA-approved drugs feature the thiazole ring, including cefiderocol[5] (fig 1.3) for multidrug-resistant infections, alpelisib[6] (fig 1.4) for HR-positive breast cancer and cobicistat (fig 1.5), an HIV therapy booster[7].

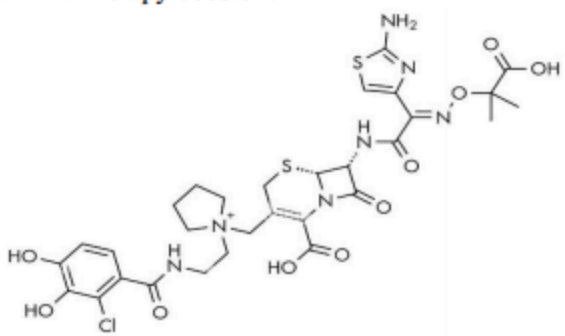

Fig 1.3 molecular structure of Cefiderocol

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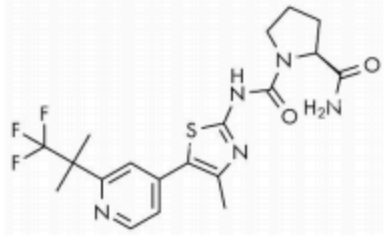

Fig 1.4 molecular structure of Alpelisib

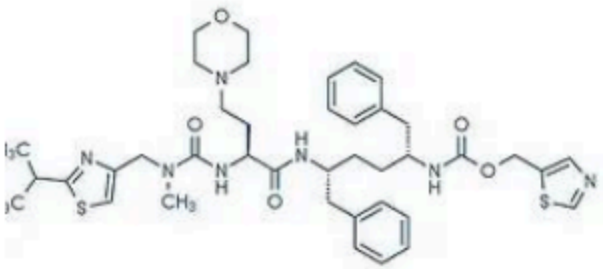

Fig 1.5 molecular structure of Cobicistat

This review explores the structural characteristics, synthetic strategies and therapeutic significance of thiazole derivatives, emphasizing recent developments in SAR, molecular docking and targeted drug design.

2. Structural Features of Thiazole: Thiazole is a five-membered aromatic heterocycle composed of a sulfur atom at position 1 and a nitrogen atom at position 3. Its aromaticity results from a delocalized π-electron system following Huckel's rule, which contributes to the molecule's planarity and resonance stabilization—properties critical for molecular recognition and target binding[4]. The nitrogen atom donates a lone pair into the aromatic sextet, while sulfur's lone pair participates less extensively, resulting in an asymmetric electron distribution across the ring[2]. Thiazole exhibits a low pKa (~2.5), indicating weak basicity and has a dipole moment around 1.17 D, reflecting moderate polarity and the potential for hydrogen bonding and membrane permeability. The C-2 position is electrophilic and often targeted in nucleophilic substitution reactions, while the C-5 position shows nucleophilic character and can undergo electrophilic attack, enabling diverse chemical modifications. These electronic features, along with its small size and conformational rigidity, enhance its ability to improve ADMET (absorption, distribution, metabolism, excretion and toxicity) properties, making thiazole a privileged scaffold widely used in rational drug design[7].

3. Synthetic Approaches to Thiazole:

3.1 Classical Methods: The synthesis of thiazole derivatives dates back to the classical Hantzsch synthesis, a widely used method involving the cyclocondensation of α-haloketones with thioamides or thiourea to yield 2,4-disubstituted thiazoles. This reaction proceeds under mild conditions and remains popular due to its simplicity and efficiency. Another important classical method is the Cook–Heilborn synthesis, which involves the reaction of acylaminonitroalkenes with thiourea derivatives. Both methods have contributed significantly to thiazole chemistry by allowing the introduction of diverse substituents and maintaining good regioselectivity[8].

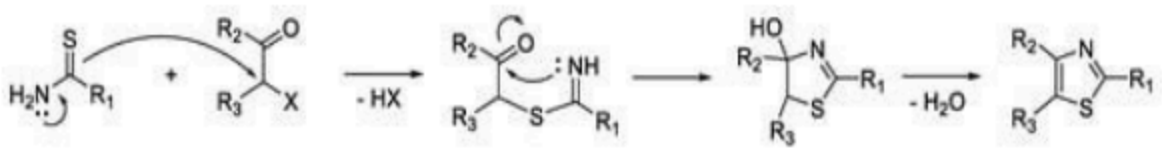

Fig 1.6 Reaction mechanism of Hantzsch thiazole synthesis.

Another method is Gabriel synthesis (fig 1.7), which consists of the cyclization reaction of acylaminocarbonyl compounds and a stoichiometric amount of phosphorus pentasulfide[9]. Cook–Heilbron synthesis (Fig 1.7) leads to 2,4-disubstituted 5-aminothiazole derivatives by the reaction of an α-aminonitrile and dithioacids or esters of dithioacids, carbon disulfide, carbon oxysulfide or isothiocyanates under mild reaction conditions[10].

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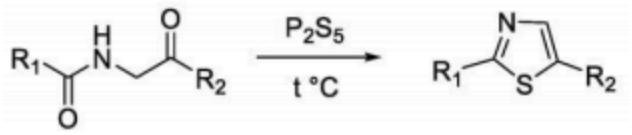

Fig 1.7 Gabriel thiazole synthesis.

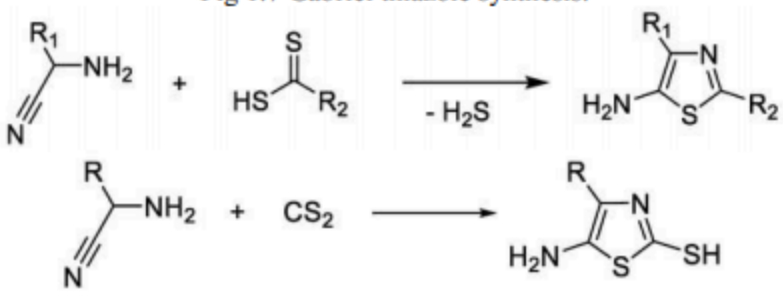

Fig 1.7 Cook–Heilbron synthesis

3.2 Green and Modern Approaches: In recent years, environmentally sustainable and energy-efficient methods have been developed for thiazole synthesis. Green synthesis strategies include solvent-free reactions, microwave-assisted synthesis and ultrasound-promoted methods that reduce reaction times and eliminate the use of toxic reagents. Metal-catalyzed protocols using catalysts like Cu, Pd or Zn, as well as ionic liquids, have been employed to improve atom economy and yields while minimizing environmental impact. These methods align with the principles of green chemistry and are increasingly favored in large-scale pharmaceutical synthesis.
Chinnaraja and Rajalakshmi reported the microwave-assisted synthesis of novel hydrazinyl thiazole derivatives[11].

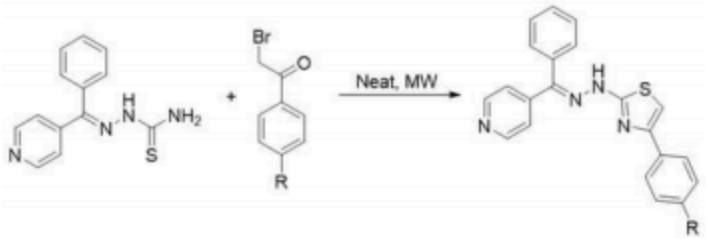

Fig 1.8 Synthesis of thiazoles from thiosemicarbazones and α-bromoketones under microwave irradiation.

Mamidala et al. reported the synthesis of new coumarin-based thiazole derivatives, starting from thiocarbohydrazide, aldehydes and α-halocarbonyl coumarins in a molar ratio of 1:2:1, under microwave heating[12].

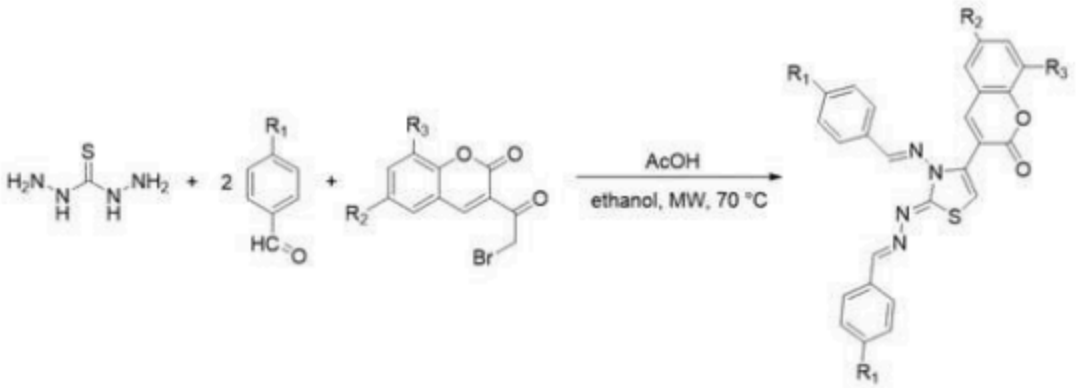

Fig 1.9 Synthesis of thiazoles from thiocarbohydrazide, aldehydes and α-bromoketones under microwave irradiation.

4 Thiazole as a Core in Drug Design: Thiazole, a five-membered heteroaromatic ring containing both nitrogen and sulfur, serves as a privileged scaffold in drug design due to its unique electronic and structural properties[14-15]. Acting as a bioisostere for phenyl, imidazole or oxazole rings, thiazole enables pharmacophoric replacement that often enhances biological activity or selectivity. Its planar and rigid conformation imparts conformational stability, which is crucial for fitting into the active site of biological targets with precision[16-17]. Additionally, the heteroatoms in thiazole facilitate hydrogen bonding interactions with amino acid residues,

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improving binding affinity. The aromatic nature of the ring supports π–π stacking interactions, particularly important in targeting nucleic acids or aromatic residues in proteins. These characteristics significantly influence the structure–activity relationship (SAR), where minor substitutions on the thiazole ring can drastically alter potency, selectivity and pharmacokinetics. Thus, the inclusion of thiazole enhances the structural and functional diversity of drug candidates across therapeutic classes.

Several clinically important drugs (fig 1.10) incorporate a thiazole ring as a core structural component, contributing to their biological activity. For example, sulfathiazole exhibits antibacterial properties as a sulfonamide derivative[18]. Aztreonam, a monobactam antibiotic and multiple cephalosporin derivatives such as ceftaroline, cefepime, cefotaxime, ceftriaxone and ceftazidime possess thiazole moieties and show broad-spectrum antibacterial activity[19]. The antiparkinsonian drug pramipexole and the antithrombotic agent edoxaban, also feature thiazole rings[20]. Isavuconazole, an antifungal triazole, incorporates a thiazole component, enhancing its interaction with fungal cytochrome P450[21]. H_2-receptor antagonists like famotidine and nizatidine use the thiazole scaffold for antiulcer effects. The nonsteroidal anti-inflammatory drug meloxicam also relies on thiazole for COX-2 selectivity (Meanwell, 2011). Antitumor agents such as tiazofurin, dabrafenib, dasatinib, ixabepilone and epothilone contain thiazole rings that enhance receptor binding or cytotoxicity. Additionally, mirabegron, a β_3-adrenergic agonist, nitazoxanide and thiabendazole (antiparasitic agents) and febuxostat, used in the treatment of gout, further exemplify the medicinal versatility of thiazole-containing compounds[22].

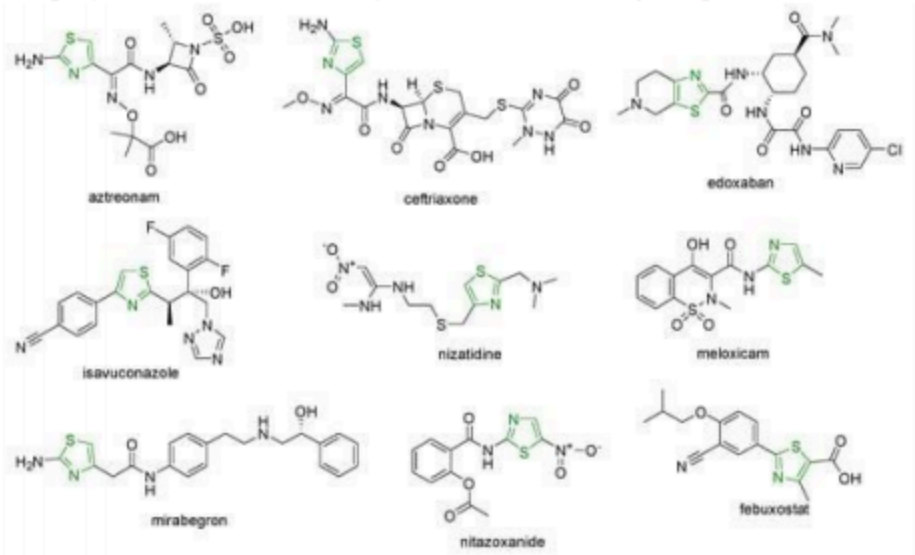

Fig 1.10 Clinically important drugs

5 Pharmacological Activities of Thiazole Derivatives: Thiazole derivatives exhibit a broad spectrum of pharmacological activities due to their versatile chemical scaffold and ability to interact with various biological targets. Their pharmacological significance spans antimicrobial, anticancer, antiviral, anti-inflammatory and neuroprotective domains, supported by structure–activity relationship (SAR) findings and mechanistic studies.

5.1 Antibacterial and Antifungal Agents: Thiazole-containing compounds have proven highly effective in combating bacterial and fungal infections, primarily through disruption of essential biosynthetic pathways. Among these, cephalosporins such as ceftriaxone and cefepime, as well as the monobactam antibiotic aztreonam, are well-established β-lactam antibiotics that act by binding to penicillin-binding proteins (PBPs). This binding inhibits the final transpeptidation step in bacterial cell wall synthesis, leading to cell lysis and death. The incorporation of a thiazole ring in these molecules enhances antibacterial potency and modulates resistance profiles. Structure–activity relationship (SAR) studies have shown that substitutions at the C-2 position of the thiazole ring significantly influence the antibacterial spectrum, stability against β-lactamases and pharmacokinetic behavior. On the antifungal front, isavuconazole serves as a potent triazole antifungal that includes a thiazole moiety in its structure. It targets lanosterol 14α-demethylase (CYP51), a key cytochrome P450 enzyme in the ergosterol biosynthesis pathway. The thiazole ring in isavuconazole coordinates with the heme iron of CYP51, thereby blocking ergosterol production—a critical component of fungal cell membranes—ultimately leading to growth inhibition and cell death.

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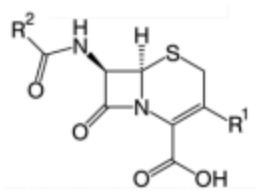
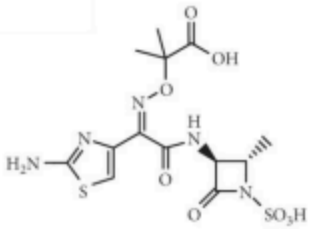
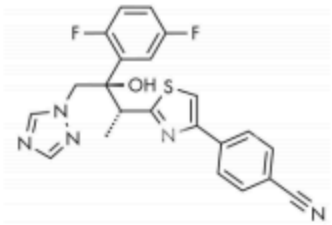


Cephalosporins

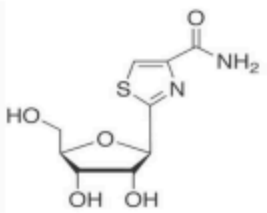


Aztreonam

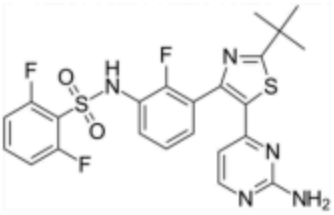


Isavuconazole

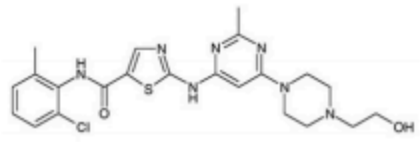
5.2 Anticancer Agents: Thiazole derivatives have shown potent antiproliferative activity through diverse mechanisms, including kinase inhibition, microtubule disruption and DNA interaction. For examples; Tiazofurin (Inhibits IMP dehydrogenase, blocks guanine nucleotide synthesis), Dabrafenib (BRAF V600E inhibitor), Dasatinib (Src/Abl tyrosine kinase inhibitor) and Ixabepilone (Binds β-tubulin and inhibits microtubule dynamics). The studies indicate substitution on the thiazole ring with hydrophobic or hydrogen-bonding groups enhances cytotoxicity and selectivity for cancer cells.



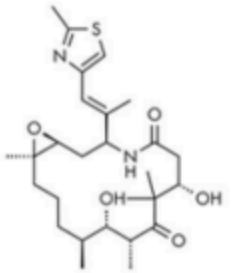
Tiazofurin



Dabrafenib



Dasatinib



Ixabepilone

5.3 Antiviral and Anti-Tubercular Agents: Thiazole derivatives have demonstrated significant antiviral and anti-tubercular activity due to their ability to interfere with essential enzymatic and metabolic processes in pathogens. Notably, nitazoxanide, a clinically approved thiazole-based compound, acts by targeting the pyruvate–ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer system, which is crucial for energy metabolism in anaerobic organisms and protozoa. This mechanism leads to the disruption of intracellular redox balance, ultimately impairing viral maturation and parasite survival. In the context of tuberculosis, thiazole-linked benzimidazole derivatives have emerged as promising candidates that exert potent inhibitory activity against the decaprenylphosphoryl-β-D-ribose 2′-epimerase (DprE1) enzyme, a validated target involved in the biosynthesis of the mycobacterial cell wall. By blocking this enzyme, these molecules prevent the formation of arabinogalactan, an essential component of *Mycobacterium tuberculosis* cell walls, thereby impairing bacterial growth and viability. Furthermore, thiazole–quinolone hybrids have shown potent anti-HIV activity, primarily through inhibition of HIV integrase, an enzyme necessary for viral DNA integration into the host genome. These compounds demonstrated IC_{50} values ranging from 0.2 to 1.2 μM, indicating high potency. Mechanistically, these agents interfere with DNA replication and electron transport processes, making them attractive scaffolds for the development of new anti-infective agents with broad-spectrum efficacy.

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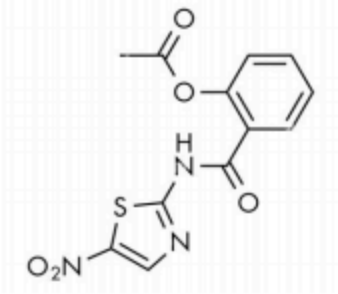
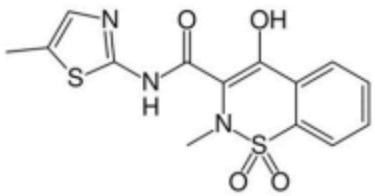


Nitazoxanide

5.4 Anti-inflammatory and Analgesic Agents: Thiazole derivatives have shown considerable promise as anti-inflammatory and analgesic agents, primarily by targeting key mediators in the inflammatory cascade. A prominent example is meloxicam, a nonsteroidal anti-inflammatory drug (NSAID) that incorporates a thiazole ring and selectively inhibits cyclooxygenase-2 (COX-2) over COX-1, thereby reducing prostaglandin synthesis responsible for pain and inflammation. With an IC_{50} of 0.015 μM for COX-2, meloxicam offers effective anti-inflammatory action while minimizing gastrointestinal side effects typically associated with nonselective NSAIDs. Structure–activity relationship (SAR) studies indicate that substitution at the C-2 position of the thiazole ring with methyl or aryl groups enhances COX-2 selectivity by improving binding interactions within the enzyme's hydrophobic pocket. Beyond COX inhibition, thiazole derivatives such as thiazolylhydrazones have shown potent anti-inflammatory potential through alternative mechanisms, notably by inhibiting pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and inducible nitric oxide synthase (iNOS). For instance, thiazolyl–pyrazole hybrids demonstrated significant TNF-α inhibitory activity, with reported IC_{50} values around 3.5 μM, making them attractive candidates for the treatment of chronic inflammatory conditions such as rheumatoid arthritis and inflammatory bowel disease.



Meloxicam

5.5 Antioxidant, Antidiabetic and Neuroprotective Agents: Thiazole-based compounds have been widely investigated for their potential in addressing oxidative stress, metabolic disorders and neurodegenerative diseases due to their versatile interactions with biological targets. As antioxidants, thiazole derivatives bearing electron-donating substituents (e.g., hydroxyl, methoxy or amino groups) exhibit potent free radical scavenging abilities, particularly against 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals, with reported IC_{50} values ranging from 5 to 10 μM, highlighting their therapeutic relevance in oxidative stress-related pathologies. In the context of antidiabetic activity, thiazole–thiazolidinone hybrids have been shown to activate peroxisome proliferator-activated receptor gamma (PPAR-γ) and inhibit α-glucosidase, a key enzyme responsible for carbohydrate digestion. This dual action leads to improved insulin sensitivity and suppression of postprandial hyperglycemia, with notable IC_{50} values around 0.8 μM for α-glucosidase inhibition. Regarding neuroprotective effects, thiazole derivatives exhibit CNS modulatory properties. For example, pramipexole, a thiazole-based dopamine D_2/D_3 receptor agonist, is clinically used in the treatment of Parkinson's disease and acts by stimulating dopaminergic neurotransmission in the basal ganglia. Additionally, thiazole–coumarin hybrids have demonstrated neuroprotective benefits by mitigating oxidative neuronal damage and modulating acetylcholinesterase (AChE) activity, which is particularly relevant in the management of Alzheimer's disease. Collectively, these findings underscore the multifaceted therapeutic potential of thiazole derivatives across a range of chronic and degenerative disorders.Thiazole derivatives have demonstrated free radical scavenging, glucose-lowering and CNS modulatory effects.

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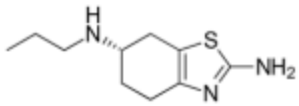

Pramipexole

6. Challenges and Future Prospects: Despite the diverse pharmacological potential of thiazole derivatives, their clinical translation is often hindered by several limitations. Key issues include poor aqueous solubility, which affects bioavailability; metabolic instability, leading to rapid degradation or short half-life in vivo; and potential toxicity, especially related to off-target effects and the formation of reactive metabolites. These drawbacks necessitate careful optimization during lead development. On the other hand, opportunities for overcoming these limitations are expanding. The design of hybrid molecules, combining thiazole with other pharmacophores, has shown promise in enhancing multi-target efficacy and pharmacokinetic profiles. Moreover, the application of artificial intelligence (AI) and machine learning in scaffold optimization, SAR prediction and ADMET profiling is revolutionizing thiazole-based drug discovery, enabling faster and more precise identification of viable candidates. Emerging areas such as targeted drug delivery systems and nanomedicine offer additional avenues for improving therapeutic index. For instance, encapsulating thiazole derivatives in nanoparticles or liposomes can enhance solubility, control release and improve targeting to diseased tissues. Thus, while challenges persist, technological innovations and interdisciplinary approaches are paving the way for the next generation of thiazole-based therapeutics.

Conclusion- Thiazole and its derivatives have proven to be structurally versatile and pharmacologically potent entities across a broad spectrum of therapeutic areas. Their five-membered heteroaromatic core, characterized by nitrogen and sulfur atoms, plays a crucial role in mediating key interactions such as hydrogen bonding, π–π stacking and conformational rigidity, which collectively enhance target specificity and binding affinity. As discussed, thiazole-based compounds exhibit diverse biological activities, including antibacterial, antifungal, anticancer, antiviral, anti-inflammatory, antidiabetic, antioxidant and neuroprotective effects, many of which are already represented in clinically approved drugs. This wide applicability reaffirms thiazole as a privileged scaffold in medicinal chemistry, valued for its ability to be finely tuned through structural modifications and hybridization strategies. Looking ahead, continued integration of computational tools, AI-guided drug design and nanotechnology-based delivery systems is expected to overcome current limitations and expand the clinical utility of thiazole derivatives. In conclusion, thiazole remains a promising framework for the development of novel therapeutics, with immense potential for innovation in the evolving landscape of modern drug discovery.

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