

Carbonic Anhydrase Inhibitors: Deciphering Pharmacological Mechanisms, Therapeutic Avenues, and Clinical Implications

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ABSTRACT

Carbonic anhydrase (CA) inhibitors hold significant promise across diverse therapeutic domains owing to their multifaceted mechanism of action. This paper delves into their therapeutic applications, highlighting their potential in cystic fibrosis by normalizing bicarbonate transport, in cancer treatment by disrupting pH balance in tumor cells, and in managing renal tubular acidosis by promoting renal bicarbonate excretion. Additionally, CA inhibitors show promise in respiratory disorders, gastrointestinal disorders, cerebral edema, migraine prophylaxis, and dry eye syndrome. Mechanistically, these inhibitors interfere with the activity of CA enzymes through reversible and irreversible inhibition, modulating pH regulation and catalytic reactions. Sulfonamide inhibitors, a subclass of reversible inhibitors, particularly target the active site of CA, showing selectivity and versatility in medical applications. Ongoing research continues to explore their potential in neurological disorders, cancer, and bacterial infections. Overall, CA inhibitors present a rich landscape for therapeutic innovation, with ongoing investigations unraveling new insights into their mechanisms and applications.

Keywords: Carbonic Anhydrase Inhibitors, Therapeutic Applications, Mechanism of Action, Reversible Inhibition, Irreversible Inhibition, Sulfonamide Inhibitors.

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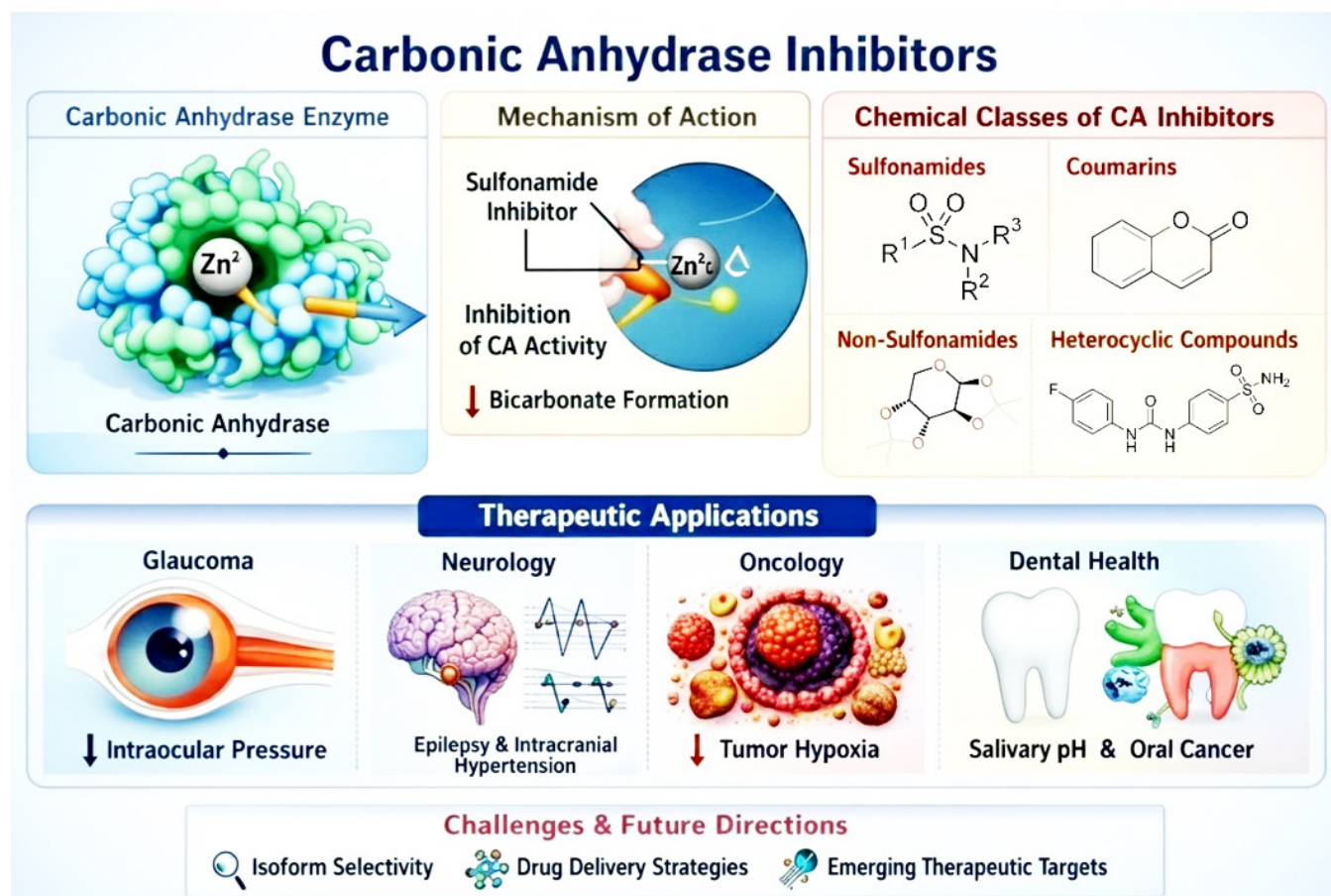
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GRAPHICAL ABSTRACT



INTRODUCTION

Carbonic anhydrases (CAs; EC 4.2.1.1) are a ubiquitous family of zinc-containing metalloenzymes that catalyze the reversible hydration of carbon dioxide to bicarbonate and protons. This seemingly simple reaction underpins a wide array of physiological processes, including acid–base homeostasis, respiration, electrolyte secretion, and biosynthetic pathways. In humans, at least sixteen CA isoforms have been identified, differing in tissue distribution, subcellular localization, and catalytic activity, thereby enabling fine regulation of pH and CO₂ transport across diverse biological systems. Dysregulation of CA activity has been implicated in numerous pathological conditions, rendering these enzymes attractive and well-validated therapeutic targets [1].

Carbonic anhydrase inhibitors (CAIs) represent one of the earliest and most clinically successful classes of enzyme inhibitors. Since the introduction of sulfonamide-based inhibitors in the mid-20th century, CAIs have been extensively utilized in the management of glaucoma, epilepsy, altitude sickness, and edema. More recently, expanding insights into CA isoform specificity have unveiled their potential in treating cancer, obesity, osteoporosis, and neurodegenerative disorders. In particular, tumor-associated isoforms such as CA IX and CA XII have emerged as critical regulators of the hypoxic tumor microenvironment, linking CA inhibition to anti-proliferative and anti-metastatic strategies [2].

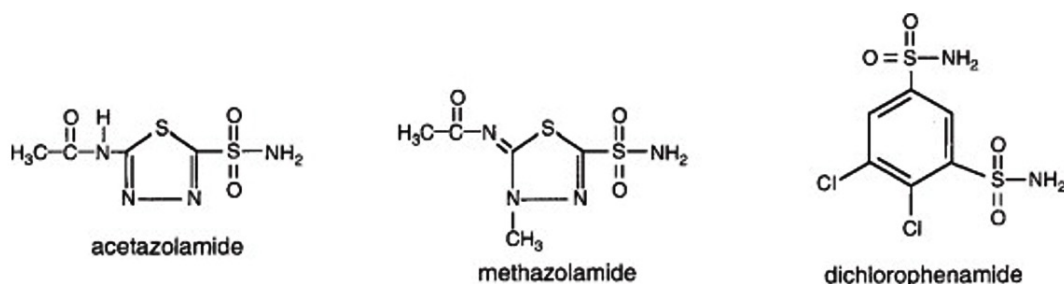


Figure 1. Classification of CA inhibitors [3].

Despite their long-standing clinical use, the pharmacological mechanisms of CAIs are far from fully elucidated. Advances in structural biology, computational modeling, and medicinal chemistry have revealed diverse inhibition modalities, including zinc-binding, non-zinc-binding, and allosteric

inhibition. These developments have catalyzed the design of next-generation CAIs with enhanced isoform selectivity, improved pharmacokinetic profiles, and reduced off-target effects—key considerations for chronic and systemic therapies [4].

Table 1. Chemical Classes and Key Sulfonamide-Based Carbonic Anhydrase Inhibitors

Chemical Class	Representative Compounds	Target CA Isoform(s)	Mechanism of Inhibition	Therapeutic Applications	Comments / Key Features
Classical Sulfonamides	Acetazolamide, Methazolamide, Dichlorphenamide	CA I, CA II	Zinc-binding, competitive inhibition	Glaucoma, Edema, Altitude sickness	Widely used clinically; non-selective
Topical Sulfonamides	Dorzolamide, Brinzolamide	CA II, CA XII	Zinc-binding, competitive inhibition	Glaucoma (ocular)	Good ocular penetration; minimal systemic effects
Aromatic/Heterocyclic Sulfonamides	SLC-0111, E7070	CA IX, CA XII	Isoform-selective zinc-binding	Oncology (tumor hypoxia targeting)	Selective for tumor-associated isoforms; experimental/clinical trials
Coumarin-based Inhibitors	Coumarin derivatives	CA I, CA II, CA IX	Non-zinc-binding, allosteric inhibition	Experimental (cancer, metabolic disorders)	Novel mechanism; potential for isoform selectivity
Non-sulfonamide CAIs	Topiramate, Zonisamide	CA II, CA VII	Mixed zinc-binding / non-zinc-binding	Epilepsy, Neurological disorders	Dual pharmacology; less potent but wider applications

This review aims to comprehensively examine carbonic anhydrase inhibitors by integrating mechanistic insights, therapeutic applications, and clinical implications. We discuss the structural and functional diversity of CA isoforms, classify major CAI chemotypes, and critically evaluate their pharmacological mechanisms. Furthermore, current clinical applications, emerging therapeutic avenues, and translational challenges are highlighted to provide a cohesive perspective on the evolving landscape of CA inhibition. By synthesizing recent advances and unresolved challenges, this review seeks to inform future research directions and facilitate the rational development of CAIs as precision therapeutics.

Therapeutic applications of inhibitors of carbonic anhydrase

• Cystic Fibrosis:

Carbonic anhydrase inhibitors are being investigated for their potential in the treatment of cystic fibrosis. The thick mucus in the airways of cystic fibrosis patients is related to abnormal bicarbonate transport, and carbonic anhydrase inhibitors may help normalize this transport and improve mucus clearance [5].

• Cancer Treatment:

Some studies suggest that carbonic anhydrase inhibitors may have a role in cancer treatment. Tumor cells often display altered pH regulation, and inhibiting carbonic anhydrase may disrupt the pH balance in cancer cells, leading to decreased proliferation and increased susceptibility to other treatments [6].

• Renal Tubular Acidosis (RTA):

RTA is a condition characterized by impaired acid secretion in the kidneys. Carbonic anhydrase inhibitors, particularly acetazolamide, are used to manage certain forms of RTA by promoting renal bicarbonate excretion and correcting acid-base imbalances [7].

• Respiratory Disorders:

Carbonic anhydrase inhibitors may have applications in respiratory disorders, such as chronic obstructive pulmonary disease (COPD) and asthma. By influencing the balance of bicarbonate and carbon dioxide, these inhibitors could potentially impact airway smooth muscle tone and bronchodilation [8].

• **Gastrointestinal Disorders:**

Carbonic anhydrase inhibitors are being explored for their potential in the treatment of certain gastrointestinal disorders. They may influence gastric acid secretion and provide benefits in conditions like peptic ulcers [9].

• **Cerebral Edema:**

Carbonic anhydrase inhibitors have been investigated for their potential in the treatment of cerebral edema, particularly in the context of traumatic brain injury and other conditions where there is an abnormal accumulation of fluid in the brain [10].

• **Migraine Prophylaxis:**

Acetazolamide, a carbonic anhydrase inhibitor, has been explored for its role in preventing migraines. The mechanism is not fully understood, but it is believed to involve cerebral blood flow regulation and changes in pH [11].

• **Ophthalmology – Dry Eye Syndrome:**

Carbonic anhydrase inhibitors are being explored for their potential in the management of dry eye syndrome. By modulating tear composition and secretion, these inhibitors may offer relief for individuals experiencing dry eye symptoms [12,13].

MECHANISM OF CARBONIC ANHYDRASE INHIBITORS

The mechanism of action of carbonic anhydrase (CA) inhibitors involves interfering with the activity of the carbonic anhydrase enzyme, which catalyzes the reversible hydration of carbon dioxide to form bicarbonate and protons. There are different types of carbonic anhydrase, but the primary focus here is on the ubiquitous and widely studied isoform, carbonic anhydrase II (CA II). CA inhibitors can be classified into two main groups: reversible and irreversible inhibitors.

Reversible Inhibition

1. *Competitive Inhibition:*

- **Binding to Active Site:** Competitive inhibitors resemble the substrate and bind to the active site of the enzyme, preventing the substrate (carbon dioxide) from binding and undergoing the normal catalytic reaction.
- **Competition for Active Site:** The inhibitor competes with the substrate for the active site, and the binding of the inhibitor is reversible.

- **Types of Reversible Inhibitors:** Sulfonamides and sulfamates are examples of reversible competitive inhibitors of carbonic anhydrase.

2. *Non-Competitive Inhibition:*

- **Binding to Allosteric Site:** Non-competitive inhibitors do not bind to the active site. Instead, they bind to an allosteric site on the enzyme, causing a conformational change that reduces the enzyme's catalytic activity.
- **Effect on Enzyme Structure:** The binding of the inhibitor alters the enzyme's structure, making it less effective in catalyzing the hydration of carbon dioxide.
- **Examples:** Some metal ions and certain derivatives of sulfonamides can act as non-competitive inhibitors.

Irreversible Inhibition

1. *Covalent Modification:*

- **Formation of a Covalent Bond:** Irreversible inhibitors form a covalent bond with the enzyme, leading to a permanent alteration of the enzyme's structure and activity.
- **Binding to the Active Site:** Some irreversible inhibitors mimic the substrate and bind to the active site, forming a covalent bond during the normal course of the catalytic reaction.
- **Types of Irreversible Inhibitors:** The anion of sulfonamide, sulfamate, and certain other compounds can act as irreversible inhibitors.

2. *Transition State Analogs:*

- **Mimicking the Transition State:** Irreversible inhibitors can be designed to mimic the transition state of the substrate during the enzymatic reaction.
- **High Binding Affinity:** These inhibitors bind more tightly to the enzyme compared to the substrate, leading to long-lasting inhibition.
- **Examples:** Certain compounds that structurally resemble the transition state of CO₂ hydration can act as irreversible inhibitors.

General Mechanisms:

1. *Catalytic Reaction Inhibition:*

- In the normal catalytic reaction, carbonic anhydrase catalyzes the reversible hydration of carbon dioxide to bicarbonate and protons.

- The inhibitors interfere with the binding of carbon dioxide, preventing its conversion to bicarbonate and protons.

2. pH Regulation:

- Carbonic anhydrase plays a crucial role in pH regulation by controlling the levels of bicarbonate and protons.
- Inhibiting carbonic anhydrase disrupts this pH regulation, impacting various physiological processes.

3. Clinical Implications:

- The inhibition of carbonic anhydrase is utilized in various therapeutic applications, such as reducing intraocular pressure in glaucoma, diuretic effects in edema, and other medical conditions [14,15].

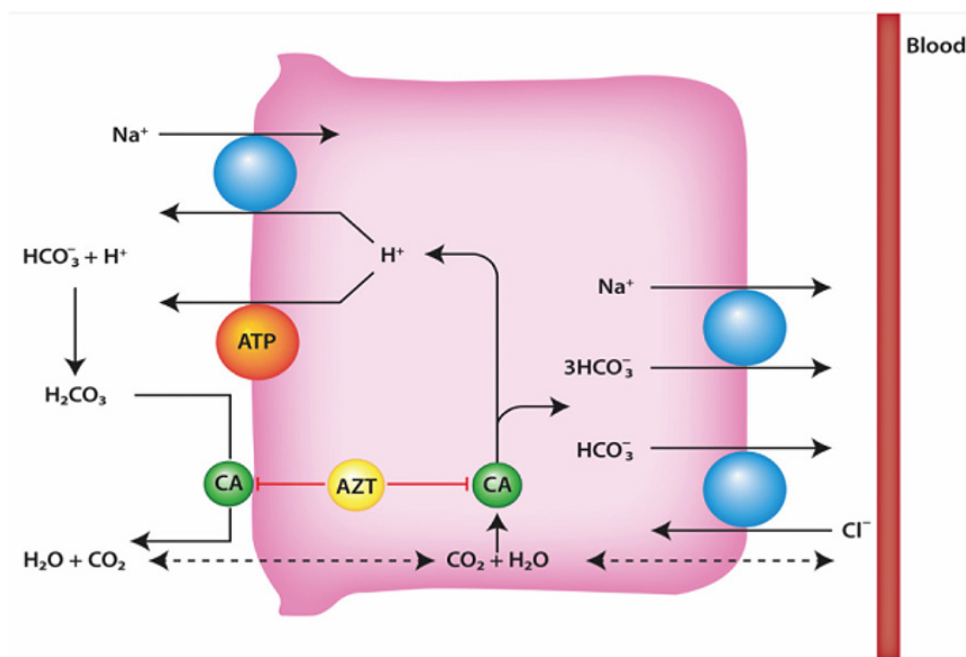


Figure 2. Mechanism of action of CA inhibitors

(cited from: <https://www.chemicalbook.com/article/the-mechanism-of-action-of-acetazolamide.htm>).

Specific Mechanism of Action of Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors exert their pharmacological effects by directly and reversibly inhibiting the zinc-containing active site of carbonic anhydrase enzymes. Carbonic anhydrases catalyze the rapid interconversion of carbon dioxide and water into bicarbonate and protons, a reaction essential for acid–base homeostasis, fluid secretion, and ion transport in many tissues. The active site of carbonic anhydrase contains a Zn^{2+} ion coordinated by histidine residues, which activates a water molecule to generate a zinc-bound hydroxide ion responsible for nucleophilic attack on carbon dioxide. Carbonic anhydrase inhibitors, particularly sulfonamide-based compounds, disrupt this catalytic process through direct coordination with the zinc ion [16].

Upon binding, the inhibitor's sulfonamide group becomes deprotonated and replaces the zinc-bound water or hydroxide

ion, forming a stable zinc–nitrogen coordination complex. This interaction blocks access of carbon dioxide to the active site and prevents formation of bicarbonate and protons, thereby halting enzymatic activity. Additional stabilization is provided by hydrogen bonding and hydrophobic interactions between the inhibitor scaffold and amino acid residues lining the enzyme pocket.

As a consequence of enzyme inhibition, physiological processes dependent on carbonic anhydrase activity are altered. In renal tubules, reduced bicarbonate formation limits sodium and bicarbonate reabsorption, increasing their excretion and leading to diuresis and mild metabolic acidosis. In secretory tissues such as the ciliary body of the eye and the choroid plexus, inhibition of carbonic anhydrase decreases aqueous humor and cerebrospinal fluid production. In the central nervous system, altered pH regulation can reduce neuronal excitability. Overall, the specific mechanism of

carbonic anhydrase inhibitors is competitive, reversible inhibition via zinc coordination, resulting in suppression of CO₂ hydration reactions and downstream changes in acid-base balance, fluid transport, and electrolyte homeostasis [17].

SULFONAMIDE INHIBITORS

Sulfonamide inhibitors are a class of reversible inhibitors that act on carbonic anhydrase (CA), specifically targeting the active site of the enzyme. These inhibitors are structurally similar to the substrate, carbon dioxide, and compete for binding at the active site. Here, I'll provide an overview of sulfonamide inhibitors of carbonic anhydrase, including their structure, mechanism of action, and therapeutic applications.

Structure of Sulfonamide Inhibitors

Sulfonamide inhibitors are characterized by the presence of a sulfonamide functional group ($-\text{SO}_2\text{NH}_2$), which is typically linked to an aromatic or heterocyclic scaffold. This functional group is the key pharmacophore responsible for inhibition of carbonic anhydrase (CA). The acidity of the sulfonamide N-H proton allows partial deprotonation under physiological conditions, enabling strong coordination with the catalytically essential Zn^{2+} ion located in the active site of CA enzymes [18].

Mechanism of Action

Sulfonamide inhibitors act through **reversible and competitive inhibition** of carbonic anhydrase by directly interacting with the enzyme's active site. Carbonic anhydrase catalyzes the rapid interconversion of carbon dioxide and water into bicarbonate and protons, a process that is critically dependent on a **zinc-bound hydroxide ion**.

Upon binding, the sulfonamide group undergoes deprotonation, allowing the **sulfonamide nitrogen to coordinate directly with the Zn^{2+} ion**, displacing the zinc-bound water or hydroxide molecule that is essential for catalysis. This interaction effectively blocks access of carbon dioxide to the catalytic center, thereby **preventing the hydration reaction**.

In addition to zinc coordination, the inhibitor is stabilized through:

- **Hydrogen bonding** with active-site residues (such as Thr, His, or Glu),
- **Hydrophobic interactions** between the aromatic or heterocyclic moiety and the hydrophobic pocket of the enzyme,

- **Van der Waals interactions** that further enhance binding affinity.

The aromatic or heterocyclic portion of the inhibitor extends into the enzyme's hydrophobic region, contributing to both **binding strength and isozyme selectivity**. Because the zinc coordination environment is highly conserved among CA enzymes, sulfonamide inhibitors exhibit high specificity toward carbonic anhydrases, although structural variations allow preferential targeting of individual isozymes [2].

Mechanistic Considerations: Zonisamide

Although zonisamide is not a classical carbonic anhydrase inhibitor, it contains a **sulfonamide moiety** that enables partial inhibition of certain CA isozymes. Zonisamide is primarily used as an **antiepileptic drug**, and its therapeutic effects are believed to arise from a combination of mechanisms, including modulation of sodium and calcium channels.

The sulfonamide group of zonisamide is thought to weakly interact with carbonic anhydrase, leading to **alterations in local pH regulation within the central nervous system**. Inhibition of CA can result in mild intracellular acidification, which may contribute to reduced neuronal excitability and seizure suppression. Although CA inhibition is not its dominant mechanism, this effect may play a **supportive role** in its overall pharmacological profile.

SIDE EFFECTS AND CONSIDERATIONS

While sulfonamide inhibitors are generally well-tolerated, they can cause side effects such as electrolyte imbalances, metabolic acidosis, and hypersensitivity reactions in some individuals. It's important to consider potential interactions with other medications and pre-existing conditions.

ONGOING RESEARCH

Research is ongoing to explore additional therapeutic applications of sulfonamide inhibitors, including their potential in treating neurological disorders, cancer, and bacterial infections [2].

CLINICAL IMPLICATIONS

Established Therapeutic Applications

Carbonic anhydrase inhibitors (CAIs) exhibit substantial clinical importance due to their central role in regulating pH homeostasis, ion transport, and metabolic processes across multiple organ systems. Several CAIs, including acetazolamide, methazolamide, dorzolamide, and brinzolamide, are clinically

approved and extensively used in the management of glaucoma, where they reduce aqueous humor production and effectively lower intraocular pressure. In neurological practice, CAIs are employed as adjunct therapies for epilepsy and idiopathic intracranial hypertension, primarily through modulation of neuronal excitability and cerebrospinal fluid dynamics. Their diuretic and acid-base regulatory properties also support their use in the treatment of edema and altitude sickness [19].

Expanding Roles in Oncology and Systemic Disorders

Beyond traditional indications, increasing attention has been directed toward the application of CAIs in oncology. Tumor-associated carbonic anhydrase isoforms, particularly CA IX and CA XII, are frequently overexpressed in hypoxic tumor microenvironments, where they facilitate extracellular acidification, tumor progression, and therapeutic resistance. Selective inhibition of these isoforms has demonstrated promising outcomes in preclinical and early translational studies, including enhanced sensitivity to chemotherapy and radiotherapy. In addition, emerging evidence suggests potential therapeutic roles for CAIs in metabolic disorders, osteoporosis, and inflammatory diseases, highlighting the broad physiological and pathological relevance of carbonic anhydrase activity [20].

Implications in Oral and Dental Health

Carbonic anhydrases are also expressed in oral and dental tissues, including salivary glands, dental pulp, and oral epithelium. Isoforms such as CA II and CA VI play essential roles in salivary bicarbonate secretion and pH buffering, processes that are critical for maintaining enamel integrity and regulating demineralization-remineralization balance. Alterations in CA activity may influence dental caries development, plaque acidogenicity, and oral inflammatory responses. Furthermore, overexpression of CA IX and CA XII has been reported in oral squamous cell carcinoma, suggesting that CA inhibition may offer adjunctive benefits in

oral oncology. Although CAIs are not currently established as standard dental therapeutics, these findings underscore their emerging relevance in oral health and disease [21,22].

Safety Considerations and Clinical Limitations

Despite their proven therapeutic value, the systemic administration of CAIs is associated with several adverse effects, including metabolic acidosis, electrolyte imbalance, paresthesia, and renal complications, which may limit long-term or high-dose use. Oral side effects, such as xerostomia and taste disturbances, are also clinically relevant, particularly in the context of dental health. These limitations emphasize the need for improved isoform-selective inhibitors and localized or targeted delivery strategies to enhance clinical efficacy while minimizing off-target toxicity.

CHALLENGES, EMERGING STRATEGIES, AND FUTURE PERSPECTIVES

A major challenge in the clinical advancement of carbonic anhydrase inhibitors is achieving high isoform selectivity, given the widespread distribution and structural similarity of CA isoenzymes. Non-selective inhibition often results in off-target effects and dose-limiting toxicity, restricting broader and chronic clinical applications. Additionally, limited tissue specificity and suboptimal pharmacokinetic profiles remain key barriers to translation, particularly for systemic and oncological indications.

To overcome these challenges, emerging strategies focus on rational drug design supported by structural biology and computational modeling. The development of non-zinc-binding inhibitors, allosteric modulators, and prodrug approaches has gained momentum as a means to improve selectivity and minimize systemic side effects. Advances in nanotechnology and targeted delivery systems offer promising opportunities for localized CAI administration, especially in cancer and potentially in oral and dental applications where site-specific modulation is desirable.

Table 2. Clinical and Emerging Applications of Carbonic Anhydrase Inhibitors

Clinical/Experimental Area	Relevant CA Isoform(s)	Representative CAIs	Mechanism / Key Effects	Clinical Status	Potential Challenges
Glaucoma	CA II, CA XII	Acetazolamide, Dorzolamide, Brinzolamide	Reduces aqueous humor secretion; lowers intraocular pressure	Clinically approved	Non-selective inhibition may cause systemic side effects
Edema / Altitude Sickness	CA II, CA IV	Acetazolamide, Methazolamide	Diuretic effect via renal pH modulation	Clinically approved	Electrolyte imbalance, metabolic acidosis
Epilepsy / Neurological Disorders	CA II, CA VII	Topiramate, Zonisamide	Modulates neuronal excitability, CSF pH	Clinically approved / adjunct therapy	CNS side effects, paresthesia
Oncology (Solid Tumors)	CA IX, CA XII	SLC-0111, Aromatic sulfonamides	Inhibits tumor-associated CA; normalizes pH in hypoxic tumor microenvironment	Preclinical / clinical trials	Isoform selectivity; tumor penetration
Oral / Dental Health	CA II, CA VI, CA IX	Experimental CAIs	Salivary pH regulation; enamel protection; tumor adjunct therapy	Preclinical / emerging research	Limited clinical translation; systemic side effects
Metabolic / Inflammatory Disorders	CA II, CA IX	Various experimental inhibitors	pH modulation affecting metabolism and inflammatory pathways	Preclinical	Isoform specificity and safety need validation
Ophthalmic / Topical Uses	CA II, CA XII	Dorzolamide, Brinzolamide	Localized pH and fluid regulation	Clinically approved	Minimal systemic absorption required

Review of Computational and Nano-Engineering Frameworks

The design and therapeutic efficacy of Carbonic Anhydrase (CA) inhibitors are increasingly dependent on sophisticated computational frameworks to predict molecular behavior and delivery stability. Early foundational work in multi-scale modeling (MSM) and high-performance computing (HPC) has provided the “computational engine” necessary for simulating these complex molecular interactions at the nano-scale [23]. Specifically, the reliability analysis of functionalized structures offers a vital blueprint for understanding the chemical stability and functionalization of sulfonamide-based nanocarriers [24]. By applying distributive computing and advanced modeling software [25], researchers can now solve high-complexity biological problems with greater precision. Furthermore, the mathematical frameworks originally developed for the reliability of nano-nodes and MEMS devices [26] are now being adapted for the “predictive design” of drug dosages, ensuring that CA inhibitors maintain their structural integrity and selectivity within the diverse pH environments of the human body.

The literature suggests that the optimization of CA inhibitors increasingly intersects with advanced computational and nano-engineering methodologies. To address the complexities of pH modulation and catalytic reaction speeds, researchers

can refer to established frameworks in High-Performance Computing (HPC) and multi-scale modeling (MSM) [23]. These methodologies provide the computational “engine” required to simulate intricate molecular interactions within the CA active site.

Furthermore, the stability of drug delivery systems is a critical factor in therapeutic success. The literature on the reliability analysis of functionalized carbon nanotubes (CNTs) [24] provides a vital blueprint for understanding how sulfonamide-based nanocarriers can be engineered for chemical stability. For the high-precision modeling required in conditions like cerebral edema or dry eye syndrome, the application of distributive computing and MATLAB-based reliability modeling [25] offers a sophisticated approach to managing high-complexity biological data.

Finally, the mathematical frameworks developed for the reliability of nano-nodes and MEMS-based systems [26] serve as a theoretical basis for “predictive design” in pharmacology. These models allow for the simulation of inhibitor integrity across the diverse and fluctuating pH environments of the human body, ensuring that selectivity and therapeutic potency are maintained from the point of delivery to the target enzyme.

Looking ahead, the future of CAI research lies in interdisciplinary integration of medicinal chemistry, nanomedicine, and translational pharmacology. Isoform-

specific biomarkers, omics-based profiling, and personalized therapeutic strategies are expected to refine patient selection and optimize treatment outcomes. Combination therapies involving CAIs with chemotherapeutic agents, immunotherapies, or metabolic modulators may further enhance efficacy and overcome resistance mechanisms. Continued exploration of carbonic anhydrase biology across systemic and oral tissues will be critical for expanding therapeutic indications and translating experimental advances into clinically viable precision medicines.

CONCLUSION

Sulfonamide-based inhibitors of carbonic anhydrase (CAIs) have long been recognized as pivotal agents in the management of several medical conditions, including glaucoma, edema, and altitude sickness. By modulating bicarbonate concentrations and regulating pH homeostasis, these inhibitors influence key physiological processes, rendering them effective in conditions characterized by dysregulated acid–base balance. Beyond their established clinical applications, ongoing research continues to provide deeper insights into their molecular mechanisms, isoform specificity, and potential therapeutic roles in emerging areas such as oncology, metabolic disorders, and oral health. As with all pharmacological agents, the use of sulfonamide CAIs requires careful consideration of patient-specific factors, clinical indications, and potential adverse effects to ensure safe and effective therapy [27].

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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