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REVIEW ARTICLE

Carbonic Anhydrase Inhibitors: Emerging Bi-Functional Agents in Cancer Therapy and Antimicrobial Resistance

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ABSTRACT

Carbonic anhydrases (CAs) are a family of metalloenzymes that catalyze the reversible hydration of carbon dioxide, playing critical roles in physiological pH regulation, ion transport, and biosynthetic pathways. Aberrant expression of specific CA isoforms, notably CA IX and XII in tumors and CA II and others in pathogenic bacteria and fungi, has positioned these enzymes as attractive drug targets in both oncology and infectious diseases. Carbonic anhydrase inhibitors (CAIs), traditionally used in the treatment of glaucoma and other non-infectious disorders, have recently gained attention for their dual therapeutic potential as anticancer and antimicrobial agents. This review explores the expanding landscape of CAIs, examining their mechanisms of action, isoform selectivity, and therapeutic implications in cancer and antimicrobial resistance. We highlight recent advances in the design of selective CAIs that exploit the tumor microenvironment and microbial survival mechanisms, with emphasis on sulfonamides, coumarins, and hybrid scaffolds. Furthermore, we discuss the challenges of drug resistance, bioavailability, and off-target effects, along with promising strategies for enhancing CAI specificity and efficacy. By bridging cancer therapy and infectious disease treatment, CAIs represent a promising class of multifunctional therapeutics. Their continued development may lead to novel interventions capable of addressing two of the most pressing global health challenges: cancer progression and antimicrobial resistance.

Keywords: *Carbonic Anhydrase Inhibitors (CAIs), Anticancer agents, Antimicrobial resistance, CA IX and CA XII, Enzyme inhibition, Dual-function therapeutics, Isoform selectivity, Drug repurposing*

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INTRODUCTION

The ubiquitous zinc enzymes known as carbonic anhydrases are found in both prokaryotes and eukaryotes. They are encoded by four different and evolutionary unrelated gene families: the carbonic anhydrases (CAs) that are found in vertebrates, bacteria, algae, and the cytoplasm of green plants; the CAs that are mostly found in bacteria, algae, and chloroplasts of both mono- and dicotyledons; the CAs that are mostly found in Archaea and some Bacteria; and the CAs that are found in some marine diatoms. Mammals have sixteen distinct CA isozymes, also known as CA-related proteins (CARP), each of which has a remarkably varied tissue distribution and subcellular location. There exist multiple cytosolic forms (CA I–III, CA VII), four membrane-bound isozymes (CA IV, CA IX, CA XII, and CA XIV), one mitochondrial form (CA V), and a secreted CA isozyme (CA VI). The interconversion of carbon dioxide and the bicarbonate ion is a very basic physiological reaction that these enzymes catalyze. As a result, they play a vital role in many physiological processes related to respiration, the transport of CO_2/bicarbonate between metabolizing tissues and the lungs, pH and CO_2 homeostasis, electrolyte secretion in a variety of tissues and organs, biosynthetic reactions (including gluconeogenesis, lipogenesis, and ureagenesis), bone resorption, calcification, tumorigenicity, and numerous other physiological or pathologic processes.

Numerous of these isozymes are targets for the development of clinically useful inhibitors or activators (1).

Figure 1 Carbonic anhydrase

In many, additional pathophysiological processes as well as fluid balance, calcification, pH regulation, carboxylation reactions, tumorigenicity, bone resorption, and the creation of HCO_3, they play critical physiological and pathological roles. Reversible hydration of carbon dioxide (CO_2) and water (H_2O) to bicarbonate (HCO_3) and a proton (H^+) is catalyzed by the CA [2].

$$CO_2 + H_2O \Leftrightarrow H_2CO_3 \Leftrightarrow HCO_3{}^- + H^+$$

A compound that interacts with an enzyme to reduce its activity is known as an enzyme inhibitor. An inhibitor can obstruct catalysis by preventing a substrate from attaching to the enzyme's active site. The mechanism by which CA inhibitors (CAIs) attach to a catalytic zinc ion ($Zn2^+$) in the CA isoenzyme's active site and prevent it from functioning is widely understood. For the treatment of mountain sickness, gastric and duodenal ulcers, neurological problems, or osteoporosis, CAIs have been shown to be clinically effective as antiglaucoma, anticonvulsant, diuretics, and antiobesity medications. Furthermore, CAIs have lately been employed as a management tool for hypoxic malignancies. Clinical derivatives of acetazolamide (AZA), an inhibitor of CA used to treat glaucoma, idiopathic intracranial hypertension, epilepsy, and altitude sickness, were the first heterocyclic and aromatic sulfonamides to be implemented in clinical settings. The process involves moving an H^+ from the active site into the solvent in order to rebuild the basic form of CA isoenzyme. Based on acetazolamide (AZA), a well-known CAI, the first synthetic heterocyclic and aromatic sulfonamides were employed in medicine. An inhibitor of CA, AZA is used to treat altitude sickness, glaucoma, epilepsy, and idiopathic intracranial hypertension. An H^+ must go from the active site to the solvent in order for the CA isoenzyme to regenerate in its basic form. Either active site residues or the buffers that are currently in the reaction media can assist this H^+ transfer. H2O resides in the fourth position, which is catalytically inactive and has an acidic pH. An H2O molecule binds to $Zn2^+$ in the CA active site at a higher pH. This proton transfer reaction then leaves a –OH group behind by transferring an H^+ to the solvent. (3)

Table 1: Distribution, localization, and catalytic activity of human carbonic anhydrase (CA) isoforms

Organ/tissue distribution	CA isoforms	Catalytic activity (CO_2 hydration)	Subcellular localization
Erythrocytes, gastrointestinal tract, and eye	CA I	Low	Cytosol
Erythrocytes, eye, gastrointestinal tract, bone osteoclasts, kidney, lung, testis, and brain	CA II	High	Cytosol
Skeletal muscle and adipocytes	CA III	Very low	Cytosol
Kidney, lung, pancreas, brain capillaries, colon, heart muscle, and eye	CA IV	Medium	Membrane-bound
Liver	CA VA	Low	Mitochondria
Heart and skeletal muscle, pancreas, kidney, spinal cord, and gastrointestinal tract	CA VB	High	Mitochondria

Salivary and mammary gland	CA VI	Low	Saliva and milk secretion
Central nervous system (CNS)	CA VII	High	Cytosol
CNS	CA VIII	Acatalytic	Cytosol
Tumors and gastrointestinal mucosa	CA IX	High	Transmembrane
CNS	CA X	Acatalytic	Cytosol
CNS	CA XI	Acatalytic	Cytosol
kidney, intestine, reproductive epithelia, eye, tumors, and CNS	CA XII	Low	Transmembrane
Kidney, brain, lung, gut, and reproductive tract	CA XIII	Low	Cytosol
Kidney, brain, liver, and eye	CA XIV	Low	Transmembrane

There are 15 known CA isoforms in the α-class that are found in most mammals, including humans, as of 2005. (4) The 16th isoenzyme, CA XV, may still exist, according to Parkkila's group's analysis of genomic databases (while it is isozyme number 16, it is numbered as CA XV because there are two CA V isozymes, CA VA and CA VB). According to sequence analysis, eight species have genomic sequences encoding CA XV, which has all the amino acid residues necessary for CA activity. These species are likely to harbour an active form of this enzyme. On the other hand, it was clear from the sequence data that CA XV in chimps and humans has evolved into a pseudogene that is not processed. It was established by reverse transcriptase PCR (RT-PCR) that humans do not express CA XV. As an alternative, mouse models using RT-PCR and in situ hybridization demonstrated positive expression in the kidney, brain, and testis. An analysis of the mouse CA XV structure was conducted. Based on phylogenetic research, CA IV and mouse CA XV are linked. CA XV and CA IV are glycosylated GPI-anchored membrane proteins that bind Sulphonamide inhibitors, among other characteristics. Because of its poor catalytic activity, CA XV's CO_2 hydrase activity depended on the proper production of disulfide bridges. The amount of active enzyme produced was enhanced by both non-specific and particular chaperones. According to these findings, the first member of the α-CA gene family expressed in other species but absent in primates is CA XV. (5)

Cancer-Associated CA Isozymes Structure and Function: One of the fifteen isoforms of the carbonic anhydrase family that are expressed in almost all human cells and tissues is called CA IX. It is involved in several physiological processes that depend on the movement of water and ions as well as the maintenance of acid-base balance. The reversible hydration of carbon dioxide to protons and bicarbonate ions is catalysed by these metalloenzymes, whose activity varies from no/low to high. A variety of subcellular compartments contain the distinct isoforms, which aid in the synthesis of gasses, bodily fluids, bone resorption, and biochemical reactions. Apart from CA IX, all CA isoforms are mostly expressed in specialized cells of differentiated tissues. However, several isoenzymes are also found in specific cancers, as CA XII in kidney and breast cancer and CA II in GIST and the endothelium of brain tumours.(6) According to reports from 1992, CA IX was the first CA to be linked to cancer. Because it is overexpressed in many different types of cancer cells and is found in relatively little amounts in normal tissue (particularly the gastrointestinal tract), CA IX displays a specific expression pattern.Hypoxia greatly induces the expression of CA IX, and this is a typical characteristic of solid tumors. Hypoxia is caused by HIF (hypoxia inducible factor) attaching to a hypoxia response element in the CA9 promoter. Thus, CA IX has been suggested as a useful intrinsic marker of tumor hypoxia that might be used in clinical practice. It was later demonstrated that the second one, CA XII, was likewise identified IN a greater variety of normal tissues and coexpressed with CA IX in multiple tumor tissues. Hypoxia also causes CAXII expression, while the underlying molecular mechanism is yet unclear. (7)

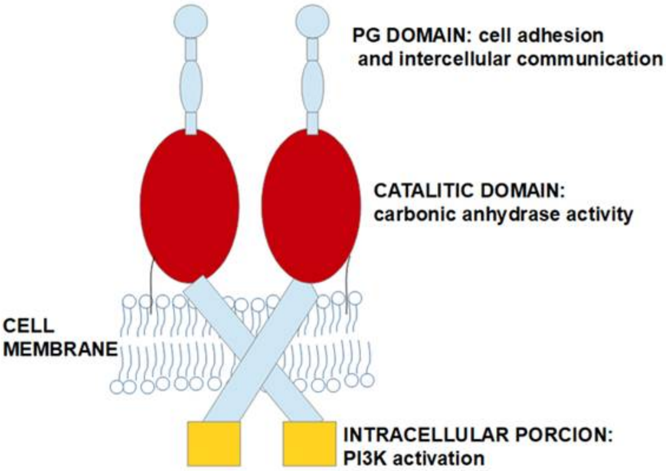

Figure 2 Structure and activity of Carbonic Anhydrase IX

In contrast to CA XII, CA IX has a distinct proteoglycan-like region at the N-terminal and forms a trimer connected by disulfide connections. Cell adhesion and differentiation have been linked to an incomplete repetitive sequence of six amino acids found in this last domain. It has been proposed that CAs use CO_2 hydration catalysis to sense and maintain the acidic tumor environment, which is an essential feature of solid tumors. Low extracellular pH has been associated with tumor progression by several mechanisms, such as chromosomal rearrangements, disintegration of extracellular matrix, invasion, migration, stimulation of cell growth factors, and activation of proteases. Acidic pH has also been associated with chemoresistance, possibly through lowering the absorption of weakly basic anticancer drugs. Anticancer drugs enter cells primarily through passive diffusion or active transport, from which they are often further processed. Anticancer medication cytotoxic activity may be dependent on both intracellular and extracellular pH because all of these activities are pH sensitive. Bicarbonate is also necessary for the production of pyrimidine nucleotides, which implies that tumor-associated isozymes are likely supplying the bicarbonate that cells need as a growth substrat. (8)

Microbial Inhibition of carbonic anhydrases: Antimicrobial resistance (AMR) has been seen to arise and spread as a result of abuse and overuse of antibiotics, despite the fact that their use helped control a number of infectious diseases. Multidrug resistance is one of the most significant risks to world health that exist now in several major diseases. Treatment for infections resulting from resistant microbes is challenging and typically involves expensive and occasionally harmful substitutes for standard medications. If greater efforts aren't taken to protect presently prescribed medications and to step up the hunt for novel antimicrobial agents, AMR-related issues are predicted to worsen. Enzymes from the superfamily Carbonic Anhydrase (CAs) have recently come to light as possible targets for drugs in diseases resistant to antibiotics. The conversion of carbon dioxide to bicarbonate and protons is a straightforward yet physiologically significant process that is catalysed by these enzymes. (9) However, because they are not selective for the human CA isoforms, their development as antimicrobial medicines is hindered by their side effects. The 15 distinct a-class isoforms that are expressed in a variety of human tissues and organs account for the side effects that are associated with the use of CAIs as treatments, including arrhythmia, kidney stone deposition, hepatic cirrhosis, and metabolic acidosis. Regretfully, no CAI that specifically targets solely microbial isoforms exists as of yet. Therefore, it would be extremely beneficial to discover highly selective inhibitors for pertinent microbial CAs in order to: (i) lessen the off-targeting of the human isoforms, which would significantly lower the incidence of side effects; and (ii) further validate CA enzymes as possible antimicrobial drug targets in therapeutic interventions against drug-resistant pathogens. (10)

Isozyme IX: Although it shares the extracellular CA domain of CA IV, this transmembrane isozyme has catalytic activity more akin to CA II. This is the first comprehensive investigation using a range of sulfonamides to inhibit CA IX. In comparison to the other isozymes (CA I, II, and IV), this one exhibits a significantly distinct inhibitory profile when exposed to the aromatic/heterocyclic sulfonamides examined here and the six clinically employed drugs. Thus, among the heterocyclic derivatives (such as the clinically used substances acetazolamide, methazolamide, ethoxzolamide, and brinzolamide), as well as the aromatic compounds very strong inhibitors (KIs less or around 40 nM) were found. Surprisingly, the most effective CA IX inhibitor found thus far is the relatively straightforward derivative 6 (3-fluoro-5-

chloro-4 aminobenzenesulfonamide, KI of 12 nm), which exhibits double the activity of acetazolamide (KI of 25 nm), the gold standard CAI. While the dihalogenated derivatives 6-14 (with inhibition constants in the range of 12-86 nm) showed significantly increased activity, the monohalogenated sulfanilamides (both acetylated and deacetylated) of types 4 and 5 generally behaved as moderate CA IX inhibitors. (11)

Aniline

Anilines ($C_6H_5NH_2$) are the compounds containing a group of amino acids ($-NH_2$) is joined to a phenyl ring (C_6H_5). It is an organic aromatic amine molecule, due to its weak basicity, it has garnered a lot of attention recently. This is ascribed to the combined action of the inductive and resonance effects. Through the inductive effect, aniline tends to pull some nitrogen electrons away from the ring because its carbon atoms are less electronegative than their nitrogen counterparts. Aniline's nitrogen atom electrons are not paired or unpaired with any other atom. If this lone pair of electrons is given to the carbon atoms, a tiny degree of resonance will be visible. As a result, the aniline has demonstrated greater resonance. Since it can contribute more electron density than it can take in, the $-NH_2$ group is an electron-donating group. However, aniline has a stronger resonance effect than an inductive one. (12)

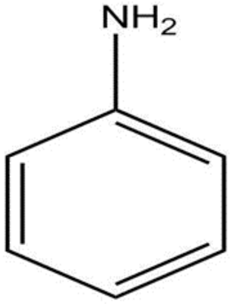

Figure 3 Aniline structure

The traditional molecular model for aromatic amines is aniline. Microwave spectroscopy has determined its structure in the gas phase, and X-ray crystallography has determined it in the solid state. Additionally, a number of theoretical investigations, including semiempirical computations, were done to ascertain. The wide range of previous studies on aniline makes it a perfect candidate to be used as a model molecule in experiments to evaluate the precision of techniques based on density functional theory (DFT) Afterwards, the most accurate technologies can be used to generalize the trends of the physicochemical properties across an animal family. (13)

The addition of a substituent group to aniline causes the molecule's charge distribution to vary, which has a significant impact on both the structural and electrical properties. Large adjustments to the excitation energies, electronic affinity, and ionization potential are especially anticipated. Over the past 50 years, a lot of study has been done on determining the excitation energy of both finite and infinite systems. Many different types of hydrogen bound compounds are formed by aniline and its derivatives. They may function as organic bases or acids by taking into account their interactions with nitrogen and oxygen atoms as donors or acceptors. (14)(15)

TABLE 2: Aniline nucleus

Molecular weight	93.12648 g/mol
Molecular formula	$C_6H_5NH_2$
Synonyms	Benzamine,Phenylamine, Aminobenzene
Melting point	−6.30 °C (20.66 °F; 266.85 K)
Boiling point	184.13 °C (363.43 °F; 457.28 K)
Density	1.02 g/cm^3
Solubility	Aniline is slightly soluble in water and mixes readily with most organic solvents.

Aniline and their derivatives: The organic production of pharmaceuticals including acetaminophen, phenacetin, acetanilide, and herbicides requires the use of aniline derivatives as essential building blocks. Several diverse applications have found use for N-alkyl anilines, such as the synthesis of dyes, polymers, and methylene diphenyl dicarbamate, which serves as a precursor to the creation of methylene diphenyl diisocyanate, an industrially significant monomer for the synthesis of rigid polyurethane. Furthermore, molecules with potent biological activities, such as antibacterial and anticancer drugs, were recognized for their derivatives, which include aromatic N-alkylamines. Aniline, phenol, and pyridine derivatives' H-bonded complexes' structural characteristics are influenced by the kind and strength of intermolecular hydrogen bonds. The scientific literature has identified and documented several hundreds of these complexes, all of which are significant in organic chemistry and biochemistry. The concept of the H-bond is introduced along with its historical evolution, and then it is addressed how H-bonds are currently classified.(16)(17)

Biological properties of Aniline Derivatives:

Antifungal agent - Aniline derivatives are used as antifungal agents like N- substituted anilines. earlier reported that N-aryl-N-[1-(hetaryl) but-3-enyl] was the identification of novel compounds with antifungal activities.2-hetaryl-4-methyl-1,2,3,4-tetrahydroquinolines (type II) and -amines (also known as "homoallylamines") (type I). In order to confirm the significance of amines as antifungal substances, it would appear suitable to evaluate the antifungal properties of a larger range of secondary amines, which are homoallylamine analogues. Furthermore, evaluating these structures as potential candidates for the synthesis of novel antifungal medicines will be made easier by comparing their cytotoxic activities and antifungal qualities. (18)

A new class of amines' physicochemical characteristics, cytotoxic, and antifungal effects: Homolylamines, N-benzyl-, N-(furylmethyl)-, N-(thienylmethyl)-, and N-pyridylmethyl-anilines (N-substituted anilines), and 2-(N-arylmethylamino)-1-furyl(thienyl) acetonitriles (a-aminonitriles) are examples of N-aryl-N-[1-(pyridyl, furyl ,or thienyl)but-3-enyl]amines (homoallylamines). Each of these substances can be categorized as an N-hetarylmethylaniline derivative because the hydrogen atom in the CH_2 group has been replaced with an allyl or nitrile group. (19)

Antimicrobial agent- Anisidine and phenolic fragments found in Schiff bases were found to exhibit notable antibacterial action. The schiff base complexes that are based on furfural (Fur) salicylaldehyde and benzimidazole derivative exhibit potent antibacterial and anticancer properties. An effective antibacterial agent against Mycobacterium TB has been demonstrated for N-(Salicylidene)-2-hydroxyaniline, a salicylaldehyde Schiff base derivative. Recent research has demonstrated the antibacterial properties of iron (III) and zinc (II) monodentate Schiff base metal complexes. The potent biological action of phenols and amines makes them significant players in medicinal chemistry. They are employed in several cellulosic applications and continue to be of interest to academics and chemists in a number of fields. (20)

The hunt for novel synthetic compounds with potent antibacterial properties never stops. The development of antimicrobial medications is essential since infections develop resistance to already available medications. The medical, pharmaceutical, food packaging, and tissue implant industries all make extensive use of polymers possessing antibacterial qualities. Potential uses of polymers in biomedicine have been made possible by their low cytotoxicity and biocompatibility. The excellent biological responsiveness of conducting polymers makes them one of the several polymer kinds that are of great interest in biomedical applications. The electroactivity, ease of synthesis, and doping-dedoping chemistry of polyaniline (PANI) make it particularly appealing. It is extensively utilized in controlled drug delivery systems, brain probes, biosensors, and tissue engineering materials. (21)

Antibacterial agent- Since antibiotics find it difficult to penetrate pathogenic cells and quickly acquire bacterial resistance, bacterial illnesses are thought to be the hardest to cure and create effective antibiotic medicines for. Agents active against Acinetobacter, Pseudomonas, and carbapenem-resistant Enterobacterales have been given top priority in research and development of antibacterial drugs by the World Health Organization. In patients with impaired immune systems, filamentous fungus and human pathogenic yeasts can produce lethal disseminated mycoses. These infections provide a significant challenge to contemporary treatment. Due to the emergence of fungal medication resistance and the emergence of novel fungal infections, including the superbug Candida auris, the situation has gotten worse in recent years. Novel prospective antifungal medication candidates are desperately needed because the available antifungal chemotherapeutics are quite restricted and some of them are rapidly losing their antifungal potency. (22)

The presence of amino groups, surface hydrophilicity, length of the polymer chain, low molecular weight, electrostatic adsorption between the PANI and bacteria, and direct contact between the material and bacterial cells have all been linked to the co-polymer of aniline's antibacterial activity. Additional research was conducted to investigate the antibacterial and antioxidant properties of conducting polymers, particularly in meta amino phenol. (23)

Anticonvulsant agent -Approximately 50 million people worldwide suffer from epilepsy, making it one of the most prevalent neurological conditions. Most cases occur in poorer nations. Estimates indicate that 20–30% of patients experience seizures that are resistant to the antiepileptic treatments that are now on the market, despite the availability of numerous new antiepileptic drugs (AEDs) and the noteworthy advancements in this field of study. Adverse effects related to dosage, including ataxia, hepatotoxicity, gingival hyperplasia, and megaloblastic anemia, are associated with the antiepileptics that are now licensed. Antiepileptic medication research therefore continues to be primarily focused on the discovery of novel, more selective, effective, and less harmful antiepileptic medicines with fewer side effects. (24)

Several pharmaceuticals that are used to treat epilepsy, including ethosuximide, phenytoin, and phenobarbital, include a heterocyclic ring with two carbonyl groups bound to a nitrogen atom. Thalidomide is an immunomodulatory medication used to treat epilepsy. A phthalimide ring linked to a glutarimide is present in the structure of thalidomide. Although thalidomide has been demonstrated to be effective in treating autoimmune, inflammatory, and erythematosis nodosum leprosum conditions, such as Crohn's disease and rheumatoid arthritis, its widespread usage is hindered by various side effects.

A series of N-aryl-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanamides derivatives were synthesized in two steps and they are used as anti-convulsant agent Phthalic anhydride and phenylalanine are first reacted under microwave radiation to form 2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoic acid, which finally took part in an amidation reaction with different anilines. (25)

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