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Benzothiadiazines in modern drug discovery: Structural insights and therapeutic applications

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Abstract
Benzothiadiazine derivatives constitute a versatile class of heterocyclic compounds with broad pharmacological potential, ranging from classical thiazide diuretics to emerging multifunctional therapeutics. The 1,2,4-benzothiadiazine 1,1-dioxide scaffold serves as the structural foundation for diverse biological activities, including diuretic, antihypertensive, antiviral, anticancer, antidiabetic, and neuroactive effects. Clinically established agents such as hydrochlorothiazide and diazoxide underscore their therapeutic importance, while newer derivatives show notable promise as antiviral agents against HCMV, HCV, and HIV, as well as neuropharmacological modulators acting positively on AMPA and kainate receptors. Recent studies also reveal potent anticancer effects, antioxidant activity, and aldose reductase inhibition, supporting their utility in addressing metabolic disorders and complications of diabetes. Insights from pharmacokinetic studies and molecular dynamics simulations further elucidate their membrane interactions, absorption, and distribution, informing future drug design strategies. This review summarizes key pharmacological activities, structure–activity relationships, and physicochemical insights of benzothiadiazines, emphasizing their evolution from traditional diuretics to a platform for multifunctional drug discovery.

Keywords: Benzothiadiazine, Antiviral Agents, Diuretic and Antihypertensive Effects

Introduction
Benzothiadiazine is a bicyclic heterocyclic compound consisting of a benzene ring fused to a thiadiazine ring containing sulfur and two nitrogen atoms. Among its derivatives, 1,2,4-benzothiadiazine 1,1-dioxides represent key scaffolds that have been extensively investigated for a wide spectrum of biological activities, including diuretic, antihypertensive, anticancer, antiviral, and neuro-modulatory effects [1, 2].

Pharmaceutical Relevance
Notable derivatives include bendroflumethiazide, chlorothiazide, cyclothiazide, hydrochlorothiazide, and diazoxide-used as diuretics, antihypertensives, or blood sugar regulators. Benzothiadiazines, particularly 1,2,4- benzothiadiazine 1,1-dioxide derivatives, are relevant in pharmaceuticals due to their diverse pharmacological activities, including diuretic, antihypertensive, antimicrobial, antiviral, antidiabetic, and anticancer properties. These compounds, and related phthalazinone-based drugs, have been used in human therapy for various conditions like hypertension, low blood sugar, and even in the treatment of HIV 3, 5[].

Scope and Focus
We'll cover emerging pharmacological applications across antiviral, anticancer, neurological, and metabolic domains.

Biological & Pharmacological Activities
Diuretic and Antihypertensive Effects
Thiazides, which are structural analogs of 1,2,4-benzothiadiazine-1,1-dioxide, are more accurately classified as benzothiadiazines. While variations exist among different thiazide compounds in terms of substituents and heterocyclic rings, they all share a common feature: an unsubstituted sulfonamide group, similar to that found in carbonic anhydrase inhibitors. Although thiazides retain some carbonic anhydrase inhibitory activity, their diuretic effect does not primarily depend on this mechanism [9, 11].

At physiological pH, thiazides exist as organic anions. Due to their high protein binding and limited filtration through the glomerulus, they must be actively secreted into the proximal tubule via a renal organic anion transporter. This secretion process competes with uric acid, which can result in elevated uric acid levels (hyperuricemia) and, in some individuals, trigger gout [11].

The main mechanism by which thiazide diuretics lower blood pressure is through inhibition of the electroneutral sodium-chloride symporter located on the apical membrane of the early distal tubule. By blocking sodium reabsorption at this site, they increase sodium delivery to the collecting duct, enhancing sodium excretion (natriuresis). This increased sodium load promotes exchange with potassium and magnesium, leading to their increased excretion and potential depletion [11].

Antiviral Potential

Benzo- and heterothiadiazine dioxides have gained recognition as important fused heterocyclic frameworks with diverse biological activities and considerable pharmacological promise. In recent years, a variety of structurally modified derivatives from this class have been identified as potent antiviral agents. Notably, substituted benzo- and heterothiadiazine dioxides have demonstrated inhibitory effects against the replication of human cytomegalovirus (HCMV), varicella-zoster virus (VZV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) [3, 17, 7].

Several highly active HCV polymerase inhibitors incorporate a benzothiadiazine dioxide scaffold, where the SO_2NH moiety plays a key role by forming strong hydrogen bonds with the enzyme's active site, thereby enhancing antiviral efficacy. Furthermore, compounds within this class have also exhibited promising antiviral activity against HCMV and VZV [3, 13].

Further investigations have led to the synthesis and evaluation of novel heterothiadiazine dioxide derivatives as potential HIV inhibitors, many of which exhibit reduced toxicity and enhanced activity against drug-resistant strains. Despite these promising findings, no comprehensive review has yet been published that systematically examines the role of thiadiazine dioxides in the development of antiviral agents.

This article aims to provide an overview of recent advancements in the antiviral potential of benzo- and heterothiadiazine dioxide derivatives, emphasizing the influence of structural modifications and insights from structure–activity relationship (SAR) studies [3].

Neurological Modulation [14]

Benzothiadiazine Derivatives as Positive Allosteric Modulators of AMPA and Kainate Receptors. Glutamate is the major excitatory neurotransmitter in the vertebrate central nervous system (CNS), acting through multiple receptor subtypes. Among these, ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) and kainate receptors (KARs) mediate rapid synaptic transmission and are critically involved in both physiological processes and pathological states. Although numerous small molecules have been developed as positive allosteric modulators (PAMs) of AMPARs with therapeutic potential for neurological disorders, pharmacological modulators specifically targeting KARs remain scarce.

The benzothiadiazine derivative IDRA21 has been investigated for its ability to modulate glutamate-induced currents in both native and recombinant AMPA and kainate receptors. Electrophysiological studies employing the patch-clamp technique were performed on primary cerebellar granule neuron cultures as well as HEK293 cells transiently transfected with AMPAR or KAR subunits.

IDRA21 significantly potentiated AMPAR- and KAR-mediated currents in both native neuronal cultures and recombinant expression systems. Modulatory activity was generally higher in native receptors compared to recombinant receptors, suggesting potential involvement of neuronal-specific factors such as auxiliary proteins or post-translational modifications.

In HEK293 cells expressing AMPAR subunits, IDRA21 exhibited higher efficacy at GluA1 homomeric receptors compared to GluA2, while the potency remained consistent across subunits. In recombinant KARs, IDRA21 displayed activity in the high micromolar range, with maximal efficacy observed in GluK2-expressing cells.

The enhancement of receptor-mediated currents was primarily observed during the plateau phase, indicating a reduction in receptor desensitization. This effect was evident across both AMPAR and KAR subtypes.

This study provides the first evidence that the AMPAR-targeting PAM IDRA21 is also capable of potentiating KAR activity. The observed subunit-specific efficacy may inform the development of more selective modulators. These findings contribute to a better understanding of KAR pharmacology and support further investigation of benzothiadiazine derivatives as potential therapeutic agents for CNS disorders.

Anticancer Activity [2, 4, 5]

Novel benzothiadiazine derivatives have been discovered with enhanced cytotoxic effects against 22Rv1 prostate cancer cells. Several of these derivatives also displayed marked inhibition of cell survival in MDA-MB-468 triple-negative breast cancer cells, highlighting their potential as promising anticancer candidates. Importantly, these compounds demonstrated higher selectivity toward MDA-MB-468 cells compared to low-tumorigenic HEK293 cells, while exhibiting superior potency and selectivity relative to the clinically employed agent 5-fluorouracil.

Antioxidant and Aldose Reductase Inhibition [1]

A series of multifunctional benzothiadiazine derivatives were synthesized and evaluated for their inhibitory activity against the enzyme aldose reductase, as well as their *in vitro* antioxidant properties, with the aim of identifying potential therapeutic agents for diabetes and its associated complications. Most of the synthesized compounds demonstrated significant aldose reductase inhibition. Notably, several derivatives also exhibited strong antioxidant activity. One compound, in particular, showed exceptional performance in both DPPH radical scavenging and malondialdehyde (MDA) inhibition assays. At concentrations of 100 μM, 10 μM, and 1 μM, this compound achieved DPPH radical scavenging rates of 98.0%, 92.3%, and 42.1%, respectively. Furthermore, its initial reaction rate at 10 μM exceeded that of Trolox, indicating superior antioxidant efficiency.

Pharmacokinetic activity

Absorption & Distribution

Oral Bioavailability

Hydrochlorothiazide is well absorbed with a bioavailability of approximately 65–75%, reaching peak plasma levels (T_{max}) in 1–5 hours.

Chlorothiazide, when given intravenously, acts quickly (peak effect in ~30 minutes), but has poor oral absorption.

Distribution

Hydrochlorothiazide has a volume of distribution ranging from 0.83–4.19 L/kg, and is 40–68% plasma protein bound.

Generally, thiazide diuretics bind significantly to serum albumin and distribute largely through the extracellular fluid.

Metabolism & Excretion

Metabolism

Hydrochlorothiazide is not metabolized and is excreted essentially unchanged.

In contrast, *diazoxide*—a benzothiadiazine derivative—is metabolized by CYP1A2 (and to some extent CYP3A4), forming inactive metabolites that are subsequently conjugated.

Excretion & Half-life

Hydrochlorothiazide has a plasma half-life ranging from 5.6 to 14.8 hours and is eliminated largely unchanged in the urine (>95%). In contrast, diazoxide displays a longer and more variable half-life of 20 to 72 hours in adults, with urinary excretion as the main elimination pathway. Its prolonged persistence in plasma is attributed to extensive protein binding and slow clearance.

Physicochemical Insights & Membrane Interactions

1.Membrane Affinity [2]

This review highlights the molecular-level interactions of benzothiadiazine with key structural components of biological membranes, including phospholipids, cholesterol, water molecules, and ions. Gaining insight into these interactions is crucial for understanding the localization of benzothiadiazine within lipid bilayers and the mechanisms governing its penetration and association with membranes—factors that directly influence its pharmacokinetic and pharmacodynamic properties. To explore these processes, molecular dynamics (MD) simulations have been conducted using model bilayers composed of dimyristoylphosphatidylcholine (DMPC), dioleoylphosphatidylcholine (DOPC), and 1,2-dioleoyl-sn-glycero-3-phosphoserine (DOPS), each supplemented with cholesterol and solvated in aqueous sodium chloride solution. These bilayer systems provide simplified yet representative models of eukaryotic membranes, capturing their essential physicochemical characteristics. Simulations were carried out under liquid-crystalline phase conditions to closely approximate physiological membrane fluidity and dynamics.

The structural and energetic data derived from these simulations—specifically radial distribution functions (RDFs), hydrogen-bonding analyses, and potentials of mean force (PMF)—provide critical insights. Benzothiadiazine displays a notable tendency to localize at the lipid–water interface, where it is energetically favored due to its amphiphilic nature. Although it can transiently dissolve into the aqueous phase, its residence time is predominantly at the membrane interface, suggesting a dynamic equilibrium influenced by both hydrophobic and polar interactions.

Hydrogen bonding plays a central role in stabilizing benzothiadiazine at the membrane. The compound is capable of forming both single and double hydrogen bonds with lipid headgroups and cholesterol hydroxyl groups.

Moreover, the PMF calculations indicate that benzothiadiazine faces an energetic barrier when attempting to translocate deeply into the hydrophobic core of the bilayer, reinforcing its preference for the interfacial region. This behavior is consistent with its moderate lipophilicity and polar functional groups, which balance its solubility between aqueous and lipid phases.

Overall, these findings suggest that benzothiadiazine preferentially associates with membrane surfaces rather than fully integrating into the hydrophobic interior, and its interaction is mediated by both hydrophobic forces and specific hydrogen bonding. This interfacial localization may influence its accessibility to membrane-bound proteins or receptors and contribute to its mechanism of action in cellular environments.

2.Hydrogen-Bond Mediated Anchoring

Key observations from in silico studies include:

Formation of single and double hydrogen bonds between DBD derivatives (at atomic sites H2 and H4) and phospholipid/cholesterol oxygen atoms, with bond lengths ranging from 1.6 to 2.1 Å.

These interactions help maintain adhesion at the membrane surface and potentially modulate diffusion dynamics.

3. Energetics and Membrane Penetration

Free-energy barrier calculations (via potential of mean force, PMF) demonstrate:

Hydrogen bonding between H2 (DBD) and lipid oxygens incurs barriers around 1–5 kcal/mol, suggesting finely balanced interactions that neither trap the molecule too deeply nor prevent entry.

Interaction

Thiazide Diuretics (e.g., Hydrochlorothiazide) — Interaction Highlights

Thiazide diuretics are associated with several clinically significant drug and condition interactions. Their concomitant use with alcohol, barbiturates, or narcotics may potentiate orthostatic hypotension, while co-administration with oral antidiabetic agents or insulin can alter glucose control, often necessitating dosage adjustments. When combined with other antihypertensive drugs, thiazides may produce additive hypotensive effects. Absorption of thiazides is substantially reduced in the presence of cholestyramine (by up to 85%) and colestipol resins (by up to 43%). Corticosteroids and ACTH may exacerbate electrolyte imbalance, particularly hypokalemia. Thiazides also reduce renal clearance of lithium, thereby increasing the risk of lithium toxicity. Nonsteroidal anti-inflammatory drugs (NSAIDs) can attenuate the diuretic, natriuretic, and antihypertensive effects of thiazides. Concurrent use with calcium supplements or vitamin D raises the risk of hypercalcemia, while licorice may potentiate hypokalemia. Additionally, in patients with systemic lupus erythematosus (SLE), thiazides may exacerbate the disease or trigger lupus-like reactions, warranting cautious use.

Diazoxide Interaction Highlights

Diazoxide is associated with multiple clinically relevant drug and condition interactions. Concomitant use with antihypertensives such as benazepril or captopril may result in additive hypotensive effects, necessitating close blood pressure monitoring. Its inhibitory action on insulin can antagonize the effects of antidiabetic agents, including insulin and metformin, thereby reducing their glucose-lowering efficacy. Co-administration with thiazide diuretics, such as hydrochlorothiazide, may further enhance diazoxide-induced hyperglycemia, while protease inhibitors including atazanavir, darunavir, and ritonavir may exacerbate its hyperglycemic effect, likely through insulin resistance. Diazoxide may also accelerate the metabolism of phenytoin, fosphenytoin, and ethotoin, leading to reduced plasma levels of these agents. When used with amifostine, additive hypotensive effects can occur, and concurrent alcohol consumption may further potentiate blood pressure reduction, increasing the risk of dizziness or fainting. In patients with renal impairment, the half-life of diazoxide is prolonged, making dosage adjustment and careful monitoring essential.

Conclusion

Benzothiadiazine derivatives have progressed far beyond their historical role as thiazide diuretics, emerging as multifunctional scaffolds with broad therapeutic potential. Advances in synthetic chemistry, structure–activity relationship analyses, and computational modeling have expanded their applications to antiviral, anticancer, neurological, and metabolic domains. Their ability to engage in diverse molecular interactions—including hydrogen bonding at membrane interfaces and selective receptor modulation—underscores their pharmacological versatility. However, challenges remain in optimizing bioavailability, reducing off-target effects, and translating preclinical findings into clinical success. Future research should integrate rational drug design with computational simulations, targeted delivery approaches, and rigorous pharmacological evaluation to fully realize the therapeutic promise of benzothiadiazine derivatives.

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