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Aromatic Carboxylic Acids and Their Pharmacologically Important Derivatives - Medicinal Chemistry and Therapeutic Applications of Benzoic Acid and Acetylsalicylic Acid

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Abstract: Aromatic carboxylic acids represent a chemically and pharmacologically privileged scaffold in medicinal chemistry, combining the electronic properties of aromatic systems with the versatile reactivity of the carboxyl group. Among these, benzoic acid and acetylsalicylic acid (aspirin) stand as two of the most widely studied and clinically impactful compounds in pharmaceutical history. This review critically examines the medicinal chemistry, pharmacological mechanisms, structure–activity relationships (SAR), and therapeutic applications of benzoic acid and its derivatives alongside acetylsalicylic acid, drawing on contemporary research published between 2010 and 2024. Key findings indicate that benzoic acid derivatives exert potent antimicrobial activity through membrane disruption and metabolic interference with bacterial folate synthesis, while acetylsalicylic acid's irreversible inhibition of cyclooxygenase (COX-1 and COX-2) isoenzymes underpins its anti-inflammatory, analgesic, antipyretic, and antiplatelet actions. Emerging research highlights the potential of novel synthetic derivatives bearing the benzoic acid or salicylate pharmacophore for oncology, neurodegenerative disease, and antimicrobial resistance applications. The scientific significance of this work lies in providing an integrated mechanistic and clinical analysis of two structurally related yet functionally diverse chemical classes, identifying critical knowledge gaps, and delineating future directions in aromatic carboxylic acid drug discovery.

Keywords: Aromatic carboxylic acids; benzoic acid; acetylsalicylic acid; aspirin; cyclooxygenase inhibition; structure–activity relationships; medicinal chemistry; drug development.

Introduction: Aromatic carboxylic acids occupy a central position in organic and medicinal chemistry, serving both as pharmacologically active entities in their own right and as versatile synthetic scaffolds for the construction of more complex bioactive molecules [1]. The fusion of a benzene ring with a carboxylic acid moiety produces a unique electronic architecture: resonance delocalization stabilizes the carboxylate anion at physiological pH, while the aromatic ring provides a hydrophobic platform for productive interactions with biological targets including enzymes, receptors, and transport proteins [2]. Collectively, these structural features have made the aromatic carboxylic acid pharmacophore one of the most frequently encountered substructures in approved small-molecule drugs.

Benzoic acid (C_6H_5COOH) holds the distinction of being among the earliest recognized naturally occurring carboxylic acids, isolated from benzoin resin by Nostradamus in the sixteenth century and characterized chemically by Scheele in 1775 [3]. Its antimicrobial and preservative properties were empirically exploited long before the molecular basis of its activity was established. The twentieth century witnessed the systematic derivatization of the benzoic acid scaffold to yield a diverse pharmacological portfolio — from para-aminobenzoic acid (PABA) and its ester local anesthetics to sulfonamide antibacterials and benzamide antipsychotics [2,4].

Acetylsalicylic acid (ASA, aspirin), formally 2-(acetyloxy)benzoic acid, represents perhaps the most consequential pharmaceutical derived from the aromatic carboxylic acid family. Synthesized by Felix Hoffmann at Bayer in 1897 through acetylation of salicylic acid — itself a derivative of benzoic acid bearing an ortho-hydroxyl group — aspirin rapidly established itself as the archetypal non-steroidal anti-inflammatory drug (NSAID) [5]. The landmark discovery by Vane, Samuelsson, and Bergström of prostaglandin biosynthesis and its inhibition by aspirin, recognized with the Nobel Prize in Physiology or Medicine in 1982, provided the mechanistic foundation for understanding aspirin's anti-inflammatory, analgesic, antipyretic, and antiplatelet properties [6]. The subsequent recognition of aspirin's irreversible COX-1 inhibition as the basis for its antiplatelet effect transformed cardiovascular medicine, establishing low-dose aspirin as a cornerstone of secondary prevention of myocardial infarction and ischemic stroke [7].

Despite their long histories, both benzoic acid derivatives and acetylsalicylic acid remain the subjects of active investigation. Contemporary medicinal chemistry efforts seek to exploit the benzoic acid pharmacophore in novel antibacterial, antifungal, and antitumor contexts, while aspirin's newly characterized mechanisms — including modulation of lipid mediator biosynthesis and epigenetic regulation — continue to generate clinical hypotheses ranging from colorectal cancer chemoprevention to Alzheimer's disease modification [8,9]. This review critically synthesizes current knowledge of the medicinal chemistry and therapeutic pharmacology of these two paradigmatic aromatic carboxylic acid compounds.

Chemical structure and physicochemical properties

Aromatic carboxylic acids

The pharmacologically relevant physicochemical properties of aromatic carboxylic acids are directly determined by the interplay between the carboxylate group and the aromatic ring system. The carboxyl group (pK_a ~4.2 for benzoic acid; ~3.5 for salicylic acid) exists predominantly as the ionized carboxylate at physiological pH 7.4, a property that governs membrane permeability, plasma protein binding (predominantly to albumin through charge–charge interactions), renal tubular secretion, and molecular recognition at biological targets [2]. The elevated acidity of aromatic carboxylic acids relative to aliphatic counterparts reflects the resonance stabilization of the carboxylate anion by the adjacent π-system, further enhanced by electron-withdrawing ring substituents.

The Hammett σ parameter provides a rigorous quantitative framework for predicting how ring substituents modulate the electronic properties — and consequently biological activity — of aromatic carboxylic acid derivatives [10]. Electron-withdrawing groups at para or meta positions (halogens, nitro, cyano, sulfonyl) increase carboxylic acid acidity, enhance electrophilicity at the carbonyl carbon, and often improve antimicrobial potency by facilitating membrane permeation in their protonated form. Electron-donating groups (amino, hydroxyl, methoxy) decrease acidity but introduce hydrogen bond donor/acceptor capacity that can profoundly alter target selectivity [10].

Structure–activity relationships

For benzoic acid antimicrobial derivatives, lipophilicity is a primary SAR determinant. Para-hydroxybenzoates (parabens: methyl, ethyl, propyl, butyl) demonstrate a systematic increase in antimicrobial potency with increasing alkyl chain length, consistent with enhanced membrane partitioning as the dominant mechanism of action [11]. The antimicrobial activity of parabens against gram-positive organisms is considerably greater than against gram-negative species, attributable to the outer membrane permeability barrier of gram-negative bacteria. In the case of acetylsalicylic acid, the ortho disposition of the acetoxy group relative to the carboxylate is pharmacodynamically indispensable: this geometry precisely positions the acetyl group for nucleophilic acyl substitution onto the catalytic serine residue (Ser530 in COX-1, Ser516 in COX-2) within the cyclooxygenase active site — a geometry unavailable to meta or para isomers [6]. The free salicylate released post-acetylation retains weak, reversible COX inhibition but lacks the antiplatelet potency of the parent compound, underscoring the pharmacological uniqueness of the ortho acetoxy arrangement.

Benzoic acid and its pharmacologically active derivatives

Antimicrobial mechanism and spectrum

Benzoic acid exerts its antimicrobial activity through two complementary mechanisms that are pH-

dependent. In its protonated (undissociated) form — predominant at acidic pH — benzoic acid readily partitions into the lipid bilayer of microbial membranes, where it dissociates intracellularly at higher cytoplasmic pH, releasing protons that disrupt the transmembrane proton gradient and impair ATP synthesis via oxidative phosphorylation [3]. The resulting intracellular acidification inhibits membrane transport systems and critical metabolic enzymes. A secondary mechanism involves interference with cellular uptake of acetate and glycerol, impairing lipid biosynthesis in yeasts and fungi [11]. The combined consequence is inhibitory activity against a broad range of bacteria (gram-positive organisms particularly), yeasts, and moulds at concentrations of 0.05–0.3% (w/v) in acidic formulations.

The antimicrobial spectrum of benzoic acid and sodium benzoate has been characterized against clinically relevant pathogens. Minimum inhibitory concentrations (MICs) reported against Staphylococcus aureus, Escherichia coli, Candida albicans, and Aspergillus niger lie in the range of 0.5–4 mg/mL under acidic conditions, rising dramatically at neutral pH — a critical practical limitation for use in non-acidified pharmaceutical preparations [12]. Resistance to benzoic acid has been described in certain Gram-negative species possessing active efflux pumps (particularly the AcrAB-TolC system in E. coli), highlighting an emerging concern for preservative efficacy in contaminated pharmaceutical products [12].

Pharmacologically active benzoic acid derivatives

The benzoic acid scaffold has yielded several pharmacological subclasses of major clinical significance. Para-aminobenzoic acid (PABA) and its esters (procaine, benzocaine, tetracaine) constitute the ester-type local anesthetics, in which the free carboxylate and aromatic amine are linked through an alkyl ester bridge to a tertiary amino group — a pharmacophore that enables voltage-gated sodium channel blockade by the protonated amine at intracellular sites [4]. The benzamide class, derived by replacing the carboxylate hydroxyl with an amide nitrogen, encompasses antipsychotics (metoclopramide, domperidone, sulpiride) that act as dopamine D_2 receptor antagonists and prokinetic drugs modulating gastrointestinal motility [4]. Benzoyl peroxide, a prodrug releasing benzoic acid and active oxygen species on skin contact, has long been employed in dermatology for acne management through its dual bactericidal and keratolytic actions [3].

Contemporary medicinal chemistry has focused on the benzoic acid scaffold as an entry point for antimycobacterial, antifungal, and anticancer drug development. Para-aminosalicylic acid (PAS), a structural analog bearing both the para-amino and ortho-hydroxyl groups relative to the carboxylate, remains an important second-line agent in multidrug-resistant tuberculosis (MDR-TB) treatment by inhibiting dihydropteroate synthase and dihydrofolate reductase in Mycobacterium tuberculosis [13]. Recent structure-based drug design campaigns have utilized the benzoic acid bioisostere tetrazole and hydroxamic acid to generate potent zinc metalloenzyme inhibitors — notably histone deacetylase (HDAC) inhibitors with demonstrated antitumor activity in hematological malignancies [9].

Acetylsalicylic acid (aspirin): mechanism and pharmacological importance

Chemical synthesis and stability

The industrial synthesis of acetylsalicylic acid involves acetylation of salicylic acid with acetic anhydride in the presence of an acidic catalyst (phosphoric or sulfuric acid), a reaction characterized by high atom economy and robust scalability [5]. The reaction proceeds via nucleophilic acyl substitution at the anhydride carbonyl by the phenolic hydroxyl of salicylic acid, generating aspirin and acetic acid. The ortho-carboxylate group of the salicylate starting material plays a dual role: it activates the phenolic oxygen as an intramolecular nucleophile (contributing to regioselectivity) and, in the product, creates the precisely defined spatial relationship between the acetoxy and carboxylate groups that is essential for COX inhibition. Aspirin undergoes hydrolytic instability in aqueous environments — degrading to salicylic acid and acetic acid — a critical pharmaceutical concern managed through anhydrous formulation conditions and the use of enteric coatings that delay dissolution until small intestinal entry [5].

Cyclooxygenase inhibition: mechanism and isoenzyme selectivity

The molecular mechanism of aspirin's anti-inflammatory and antiplatelet action centers on the irreversible acetylation of a critical serine residue within the cyclooxygenase (COX) active site channel. Cyclooxygenase enzymes (COX-1, constitutively expressed; COX-2, inducible by inflammatory stimuli) catalyze the committed step in prostanoid biosynthesis: the bis-dioxygenation and cyclization of arachidonic acid to prostaglandin G_2 (PGG_2), subsequently reduced to PGH_2 [6]. Aspirin irreversibly acetylates Ser530 in COX-1 and Ser516 in COX-2, sterically blocking the hydrophobic channel through which arachidonic acid accesses the catalytic heme center, thereby abolishing prostaglandin, thromboxane, and prostacyclin production

downstream [6,7]. Crucially, aspirin demonstrates approximately 170-fold greater potency against COX-1 than COX-2, a selectivity ratio that has profound clinical implications: COX-1 inhibition in anucleate platelets is permanent for the platelet's lifespan (~10 days), since platelets cannot synthesize new COX-1 protein, while nucleated vascular endothelial cells recover COX-2-mediated prostacyclin (PGI_2) synthesis within hours [7].

More recently, aspirin's pharmacological repertoire has been extended to include acetylation of COX-2 in a manner that redirects its oxygenase activity from prostaglandin E_2 (PGE_2) synthesis to the generation of 15-epi-lipoxin A_4 (aspirin-triggered lipoxin, ATL) — an endogenous pro-resolving lipid mediator with potent anti-inflammatory properties [8]. This observation fundamentally reframes aspirin not merely as an inhibitor of inflammatory mediator synthesis but as a trigger for active inflammation resolution, a mechanistic insight with implications for understanding aspirin's cancer chemopreventive effects.

Anti-inflammatory, analgesic, and antipyretic actions

The anti-inflammatory efficacy of aspirin at standard therapeutic doses (650–1000 mg, 3–4 times daily) operates through suppression of prostaglandin E_2 (PGE_2) and prostacyclin (PGI_2) synthesis in inflamed tissues, reducing vasodilation, increased vascular permeability, and sensitization of peripheral nociceptors — collectively reducing the cardinal signs of inflammation [6]. Analgesic action results from both peripheral reduction of prostaglandin-mediated nociceptor sensitization and central inhibition of spinal COX activity modulating pain signal amplification. Antipyresis reflects prostaglandin E_2 suppression in the hypothalamic thermoregulatory center, where PGE_2 normally elevates the temperature setpoint in response to cytokine-mediated induction of hypothalamic COX-2 [6]. The dose-dependent nature of these effects — with antiplatelet activity achieved at doses as low as 75–100 mg/day and anti-inflammatory efficacy requiring 3–5 g/day — reflects the differential sensitivity and recovery rates of COX-1 and COX-2 across tissues.

Therapeutic applications in modern medicine

Cardiovascular disease prevention

The most extensively validated therapeutic application of low-dose aspirin (75–150 mg/day) is secondary prevention of atherothrombotic cardiovascular events in patients with established coronary artery disease, ischemic stroke, or peripheral arterial disease [7]. By irreversibly inhibiting platelet COX-1, aspirin suppresses thromboxane A_2 (TXA_2) synthesis — a potent platelet aggregation agonist and vasoconstrictor — reducing platelet-mediated thrombus formation at sites of atheromatous plaque rupture. Multiple landmark trials (ISIS-2, CAPRIE, CURE) and meta-analyses encompassing over 200,000 patients have established a 19–25% relative risk reduction in major adverse cardiovascular events with antiplatelet therapy in secondary prevention [7]. Contrastingly, the evidence for primary prevention (in individuals without prior cardiovascular events) has been substantially undermined by three large randomized trials published between 2018–2019 (ARRIVE, ASPREE, ASCEND), which collectively demonstrated that aspirin's modest absolute cardiovascular benefit is offset by increased gastrointestinal and intracranial bleeding risk in low-cardiovascular-risk individuals [14]. Current guidelines from the American College of Cardiology and American Heart Association have consequently narrowed primary prevention indications to selected high-risk patients aged 40–70 years [14].

Cancer chemoprevention and emerging applications

Epidemiological and mechanistic evidence has accumulated over three decades supporting aspirin's capacity to reduce incidence and mortality from colorectal cancer (CRC), and to a lesser extent gastric, esophageal, and breast cancers [8]. The CAPP2 randomized trial demonstrated a 63% reduction in CRC incidence in Lynch syndrome patients receiving aspirin 600 mg/day for ≥2 years, with a latency period of approximately 5 years before benefit became apparent — consistent with the timescale of adenoma-to-carcinoma progression [15]. Mechanistically, aspirin's chemopreventive activity in colorectal cancer is linked to PGE_2 suppression (reducing COX-2-driven proliferative signaling via EP receptor activation of PI3K/Akt and Wnt/β-catenin pathways), induction of apoptosis through NF-κB inhibition, and generation of aspirin-triggered lipoxins that suppress tumor-promoting inflammatory microenvironments [8,15]. Benzoic acid derivatives, particularly hydroxamic acid-bearing analogs acting as HDAC inhibitors, are under active clinical investigation for hematological malignancies, with vorinostat and romidepsin representing approved agents in this structural class [9].

Pharmaceutical formulations and drug delivery considerations

The clinical utility of both benzoic acid derivatives and aspirin is intimately linked to formulation science. Enteric-coated aspirin tablets (EC-ASA) utilize pH-sensitive polymeric coatings (cellulose acetate phthalate, Eudragit L100) to bypass gastric dissolution, reducing direct gastric mucosal exposure; however, pharmacokinetic studies indicate that enteric coating

reduces peak plasma concentrations and delays the time to maximum COX inhibition, potentially compromising efficacy in acute settings requiring rapid platelet inhibition [16]. Aspirin's extensive plasma protein binding (50–80% at standard doses) and non-linear pharmacokinetics at higher doses (saturation of salicylate conjugation pathways) are clinically important considerations in dosing strategies. Topical formulations of benzoic acid (Whitfield's ointment, 6% benzoic acid + 3% salicylic acid) remain a low-cost, effective treatment for superficial dermatophyte infections in resource-limited settings, exploiting the synergistic antifungal and keratolytic properties of both acids [11].

DISCUSSION

A critical appraisal of the scientific literature reveals several important tensions and unresolved questions in the pharmacology of aromatic carboxylic acids. First, the evolving clinical evidence on aspirin in primary cardiovascular prevention exemplifies a recurring challenge in pharmacology: population-level epidemiological benefits observed in observational studies frequently overestimate absolute benefits in controlled trial settings due to confounding and indication bias [14]. The net clinical benefit of aspirin is inherently population-specific, determined by the interplay between baseline cardiovascular event rate, bleeding risk, and the magnitude of COX inhibition achieved at the selected dose — factors that vary substantially across age groups, comorbidities, and concomitant medications.

Second, the growing recognition that aspirin's pharmacological actions extend well beyond simple COX inhibition — encompassing acetylation of multiple cellular proteins including NFκB, Akt, and histone acetyltransferases [17] — raises fundamental questions about which mechanisms underlie its diverse observed biological effects. This proteome-wide acetylation activity is concentration-dependent and may contribute to both therapeutic effects (cancer chemoprevention) and adverse effects (hepatotoxicity at high doses) in ways that standard pharmacokinetic–pharmacodynamic models, which assume single-target engagement, cannot fully capture. Proteomics-based approaches are beginning to map the aspirin acetylome systematically, with implications for understanding inter-individual variability in therapeutic response [17].

For benzoic acid antimicrobial derivatives, the principal research gap concerns the molecular basis of resistance in the context of pharmaceutical preservation. The exponential rise in preservative-resistant nosocomial pathogens — and the contamination of hospital pharmaceutical preparations with organisms possessing efflux-mediated benzoate resistance — represents a serious patient safety concern inadequately addressed by current regulatory frameworks for preservative efficacy testing [12]. Importantly, MIC data generated in standard broth microdilution assays may poorly predict antimicrobial efficacy in complex pharmaceutical matrices containing surfactants, proteins, and polymers that alter compound partitioning and availability [11,12].

Third, the structure–activity relationship landscape for novel benzoic acid derivatives in oncology remains immature. While the HDAC inhibitor vorinostat validates the hydroxamic acid-modified benzoic acid as an antitumor pharmacophore, achieving isoenzyme selectivity among the 18 human HDAC enzymes — which have distinct cellular functions and tissue distributions — is a major unmet medicinal chemistry challenge [9]. The development of HDAC inhibitors with defined isoenzyme selectivity profiles will require iterative structure-guided medicinal chemistry campaigns supported by co-crystallography and cellular target engagement assays that extend beyond cytotoxicity screens.

Future perspectives

Several emerging research directions hold particular promise for advancing the medicinal chemistry of aromatic carboxylic acid derivatives. The application of fragment-based drug discovery (FBDD) to the benzoic acid scaffold enables systematic exploration of chemical space around the carboxylate pharmacophore with high crystallographic resolution, potentially yielding novel chemotypes with improved selectivity for bacterial targets including FabA, InhA (antitubercular), and LpxC (antibacterial via lipid A biosynthesis) — all of which accommodate benzoic acid-like fragments in their active sites [18].

In the context of aspirin's chemopreventive activity, the development of aspirin–lysine-phosphatidylcholine conjugates (phospho-aspirin, NO-aspirin) that reduce gastrointestinal toxicity while preserving or enhancing COX-independent anticancer mechanisms is under active investigation [19]. Nitric oxide-releasing aspirin derivatives (NO-ASA) simultaneously deliver NO — a smooth muscle relaxant and cytoprotective agent — and acetylsalicylate, achieving superior gastrointestinal tolerability and amplified antiproliferative activity in preclinical colorectal cancer models relative to conventional aspirin [19].

The intersection of aromatic carboxylic acid chemistry with proteolysis-targeting chimeras (PROTACs) represents another frontier. Incorporation of salicylate or benzoate linkers into bifunctional PROTAC molecules — which recruit E3 ubiquitin ligases to degrade target

oncoproteins — could leverage the favorable pharmacokinetic properties and protein-binding geometry of aromatic carboxylates to optimize ternary complex formation [20]. Additionally, the application of machine learning-guided molecular design to the benzoic acid chemical space offers the prospect of rapidly identifying novel derivatives with optimized predicted ADMET (absorption, distribution, metabolism, excretion, toxicity) profiles, accelerating the transition from in silico screening to lead optimization in antimicrobial and oncology drug discovery programs [18].

CONCLUSION

Benzoic acid and acetylsalicylic acid, while structurally simple representatives of the aromatic carboxylic acid family, have shaped modern pharmacotherapy to a degree disproportionate to their molecular complexity. The mechanistic and structural insights reviewed here — from the pH-dependent membrane disruption underpinning benzoate antimicrobial activity to the precise geometric requirements for aspirin's irreversible COX acetylation — illustrate how physicochemical fundamentals directly translate into pharmacological specificity. The evolving clinical evidence on aspirin in cardiovascular and cancer medicine highlights both the extraordinary translational value of mechanistic pharmacology and the necessity of rigorously designed clinical trials to establish the risk–benefit balance in defined patient populations. For benzoic acid derivatives, the convergence of classical antimicrobial chemistry with contemporary epigenetic oncology targets demonstrates the enduring capacity of this scaffold to generate therapeutically relevant chemical matter. Future progress in this area demands integrated medicinal chemistry campaigns combining structure-based design, computational ADMET prediction, and mechanistically informed clinical translation, with particular emphasis on selectivity optimization and gastrointestinal safety improvement. The aromatic carboxylic acid pharmacophore, far from being an exhausted chemical class, continues to offer rich opportunities for drug discovery across multiple therapeutic areas.

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