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REVIEW: Synthesis Routes from Salicylic Acid to Mesalazine; A Short Review

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ABSTRACT

This mini-review provides a chronological and mechanistic overview of synthetic developments leading from salicylic acid to mesalazine (5-aminosalicylic acid).

Historical nitration routes (1843–1954) relied on mineral acids under uncontrolled conditions, while modern approaches (2005–2025) have achieved regioselective 5-nitration with yields exceeding 85% using catalytic, microwave-assisted, or solvent-free systems. Subsequent reduction of 5-nitrosalicylic acid to its amine derivative has evolved from tin or sulfide reagents to environmentally benign catalytic hydrogenations, electrochemical, and mechanochemical protocols.

Recent industrial patents and academic studies demonstrate scalable aqueous hydrogenations with precise pH control and remarkable product selectivity. The review highlights a technological transition from classical stoichiometric transformations to green, recyclable, and nanostructured catalytic processes. Emerging research- particularly the use of solid acid supports and Zn-based nanocatalysts for efficient nitro reduction- points toward a sustainable future landscape for mesalazine synthesis, integrating high yield, process safety, and environmental responsibility within modern pharmaceutical chemistry.

Introduction

Gastrointestinal disorders, particularly ulcerative colitis and Crohn's disease, represent significant clinical challenges worldwide [1,2]. Mesalazine (5-aminosalicylic acid) has emerged as a first-line therapy due to its potent local anti-inflammatory activity in the colonic mucosa. Its therapeutic efficacy arises from the suppression of pro-inflammatory mediators, including cytokines, prostaglandins, and leukotrienes, while avoiding the systemic immunosuppression associated with corticosteroids [3]. Over the past decades, various formulations including delayed-release tablets, enteric-coated capsules, and topical enemas have been developed to optimize colonic delivery, enhance bioavailability, and improve patient adherence [4]. Beyond its conventional role in inflammatory bowel disease, mesalazine has demonstrated chemopreventive potential in colorectal cancer by modulating oxidative stress and inhibiting abnormal epithelial proliferation [5]. Such a broad pharmacological spectrum continues to stimulate research into structural modifications and combination therapies aimed at enhancing therapeutic outcomes [6]. In addition to gastrointestinal applications, mesalazine's anti-inflammatory properties have been explored in other conditions, including rheumatoid arthritis, psoriasis, and autoimmune dermatological disorders, further expanding its clinical relevance [7]. The increasing demand for mesalazine in parallel with many active pharmaceutical ingridients (API) highlights the critical importance of efficient, scalable, and sustainable synthetic routes and analysis [8,9]. High-yielding, regioselective, and environmentally benign production processes are essential to ensure consistent drug quality, minimize hazardous byproducts, and reduce cost, particularly when transitioning from laboratory-scale to industrial manufacturing [10,11]. Moreover, precise control over functional-group transformations, such as nitration and reduction, directly affects both pharmacological efficacy and safety, underscoring the need for optimized synthetic methodologies [12].

Recent advances in synthetic chemistry have enabled the development of modern strategies that integrate classical knowledge with green chemistry principles. Techniques such as catalytic hydrogenation, microwave-assisted nitration, electrochemical reduction, and mechanochemical processes offer improved efficiency, reduced reaction times, and minimal environmental impact [13]. These approaches reflect a paradigm shift from stoichiometric, heavy-metal-based transformations toward recyclable, solvent-free, and energy-efficient protocols. By systematically evaluating these methodologies, researchers can identify routes that maximize yield, selectivity, and scalability while adhering to sustainability goals [13,14].

Recognizing the critical link between pharmaceutical demand, process optimization, and sustainability, this mini-review was prepared to provide a comprehensive overview of mesalazine synthesis from salicylic acid. We summarize historical developments, mechanistic insights, and contemporary innovations that have shaped laboratory and industrial practice. Emphasis is placed on strategies that enhance regioselectivity, process safety, and environmental responsibility, highlighting how modern synthetic chemistry can support both therapeutic efficacy and sustainable pharmaceutical production [14]. The review aims to serve as a reference for chemists, pharmaceutical scientists, and process engineers seeking to advance the synthesis of mesalazine and related aminosalicylates through informed, innovative, and efficient methodologies.

Synthesis routes from Salicyclic acid to 5-nitro salicylic acid

The inaugural nitrations of salicylic acid were reported in the mid-19th century, beginning with Gerhardt and Cahours and followed by subsequent confirmations by Werther and Huebner; these classical procedures consistently employed mineral nitrating agents such as concentrated nitric acid often in acetic acid media [15–20]. Early reports rarely quantified isolated yields, yet they provided essential empirical evidence about the susceptibility of the salicylate nucleus to electrophilic aromatic substitution while preserving the benzoic acid functionality (e.g., carboxyl group stability under nitration conditions). Deninger's late-19th century contributions further refined crude condition descriptions by noting temperature control and nitrite/sulfuric acid permutations relevant to mono- versus dinitration pathways [21]. Collectively, these nineteenth-century accounts established the mechanistic baseline for regioselectivity trends- particularly the balance of ortho/para directing effects by the phenolic hydroxyl and the deactivating influence of the carboxylate- which later researchers leveraged to bias substitution toward the 5-position. These foundational studies are documented across the early reference set and remain the canonical starting point for any chronological treatment of salicylic nitration.

During the early to mid-20th century, method development shifted toward controlling selectivity and limiting side-reactions through choice of solvent and mixed-acid systems. Hirsch and Taborsky explored staged reaction sequences and the use of sulfuric–nitric mixed acids to tune electrophilicity and suppress over-nitration [22–23]. Meldola and Raiziss contributed systematic observations about aqueous versus non-aqueous media and the influence of temperature on regioisomer ratios [24–25]. By the 1920s–1950s several groups reported the benefits of alternative nitrating species (nitrosylsulfuric acid, gaseous nitrogen oxides) or non-polar co-solvents (chloroform, diethyl ether, nitrobenzene) to modulate nitration kinetics and to facilitate isolation of mono-nitro products [26–30]. These investigations, often qualitative but reproducible, connected classical organic reactivity principles with emerging physical-organic insights (reaction kinetics and solvent effects), yielding robust lab-scale procedures that informed later scale-up and industrial adaptations.

The early 21st century witnessed marked improvements in both selectivity and throughput by adopting metal-mediated nitrates and alternative activation modes. Iranpoor reported zinc-nitrate based protocols in dichloromethane with brief reaction times, while Bose’s microwave-assisted nitration using calcium(II) nitrate in acetic acid produced high isolated yields (reported up to ~84%) with dramatic time compression relative to classical methods [32–34]. Andreozzi and colleagues investigated kinetic control and reagent-system tuning (acetic anhydride co-media, sulfuric acid variations) to delineate temperature/acid-strength effects on regioselectivity [35]. Tajik et al. and Kulkarni further illustrated that phase-transfer or oxidant-modulated systems permit selective 5-nitration with reduced byproduct formation [36–37]. These advances demonstrate that replacing stoichiometric harsh nitrating mixtures with milder metal nitrate sources and controlled energy input (microwave, optimized heating profiles) can substantially improve both green credentials and process economics while maintaining or enhancing 5-nitro selectivity.

From 2010 onward, patents and academic reports converged on scalable, higher-yield protocols amenable to industrial manufacture. Industry and university patents (e.g., LONZA, Qilu University, China Petroleum Chemical, and Heilongjiang Xinchuang) document routines achieving 60–89% yields under moderated temperatures, sometimes employing recyclable acid systems, ionic liquids, micellar media or solvent-free approaches to reduce waste and hazard profiles [41, 44–48]. Noteworthy examples include ionic-liquid mediated nitrations and micellar/regioselective methods that reported yields in the high 70s to upper-80s percent range for controlled 5-nitration [50–51]. Very recent work (Dolai 2023; Hussain 2025) reiterates the trend toward solvent-economical or neat nitrations with short reaction times and acceptable yields (e.g., 74–89%) suitable for downstream hydrogenation to mesalazine precursors [52–53]. This trajectory- from empirical 19th-century recipes to 21st-century sustainable, well-characterized processes- illustrates how mechanistic understanding, alternative reagents, and engineering considerations coalesce to deliver industrially relevant routes to 5-nitrosalicylic acid.

Synthesis routes from 5-nitro salicylic acid to 5-amino salicylic acid

The earliest conversions of 5-nitrosalicylic acid to its amine analogue were reported by Schmitt (1864) using Sn/HCl or Sn in acetic acid followed by H_2S precipitation of tin sulfide [54–55]. Subsequent workers, including Huebner (1879), Minaew (1931), and Karzew (1936), extended these routes employing aqueous or basic sodium sulfide / sodium hydroxide systems at temperatures near 110 °C [19, 56, 59]. These processes, while conceptually straightforward, suffered from incomplete reductions and heavy-metal waste generation.

Table 1. Synthesis routes from Salicyclic acid to 5-nitro salicylic acid

Researcher	Year	Reagents/ condition	Yield (%)
Gerhardt [15]	1843	Nitric acid; acetic acid	-
Cahours [16]	1844		-
Werther [17]	1859	Nitric acid; acetic acid	-
Huebner [18]	1874	Nitric acid; acetic acid	-
Huebner [19]	1879	lead(II) nitrate; acetic acid or Nitric acid; acetic acid	-
Huebner [20]	1879	nitric acid; acetic acid	-
Deninger [21]	1890	sulfuric acid; water; sodium nitrite Erwaermen des Reaktionsgemischs auf 50grad; or $KNO_2+H_2SO_4$	-
Hirsch [22]	1900	Reaktion ueber mehrere Stufen or HNO_3+H2SO_4	-
Taborsky et al. [23]	1912	With sulfuric acid; nitric acid	-
Meldola [24]	1917	water; nitric acid	-
Raiziss [25]	1922	With nitric acid; acetic acid at 20°C;	-
Varma [26]	1925	nitrosylsulfuric acid; nitric acid at 30°C;	-
Baroni [27]	1936	chloroform; nitric acid	-
Marchand [28]	1954	Nitric acid; acetic acid	-
Goldberg [29]	1954	diethyl ether; mixture of gaseous nitrogen oxides	-
Hetherington [30]	1954	NO2F; nitrobenzene	-
Chawla, H. Mohindra [31]	1983	In at 50 - 60°C; for 0.25h; Further byproducts given;	37
Iranpoor, Nasser [32]	2005	Zn(NO3)2*2N2O4 In dichloromethane at 20°C; for 0.0833333h;	-
Bose, Ajay K. [33]	2006	With calcium(II) nitrate In acetic acid for 0.0166667h; microwave irradiation;	84
Bose, Ajay K. [34]	2006	at 20 - 85°C; for 0.0333333h; microwave irradiation;	72
Andreozzi, Roberto [35]	2006	nitric acid; acetic anhydride; acetic acid In water at 14.84°C; Kinetics; Temperature;	-
Andreozzi, Roberto [35]	2006	sulfuric acid; nitric acid In water at 14.84°C; for 2.25h; Kinetics; Temperature;	-
Andreozzi, Roberto [35]	2006	nitric acid; acetic acid at 24.84°C; Kinetics; Temperature; Reagent/catalyst;	-
Tajik, Hassan [36]	2007	With sodium nitrate; benzyltriphenylphosphonium peroxodisulfate In acetonitrile for 65h; Heating	70
Kulkarni, Amol A. [37]	2008	at 50°C; for 0.166667h; Temperature; Time;	-
Tasneem; ; Rajanna; Saiprakash [38]	2009	In at 24.84°C; for 2.5h; Micellar solution; regioselective reaction	89
Kalbasi, Roozbeh Javad [39]	2010	In at 40°C; for 0.0833333h; regioselective reaction;	-
Hummel, Michael [40]	2010	isopropyl nitrate; sulfuric acid; tetra(n-butyl)ammonium hydrogensulfate In dichloromethane at 35°C; Cooling with ice;	-
LONZA - US2010/298567 [41]	2010	nitric acid; acetic acid at 75°C;	-
Abdulla [42]	2011	copper(II) tetraamine sulfate; nitric acid In dichloromethane; water at 20°C; for 2.5h; regioselective reaction;	86
Galli, Francesco [43]	2011	α-tocopheramine; silver(l) oxide In hexane	13
HEILONGJIANG XINCHUANG BIOLOGICAL TECH DEV - CN106083623 [44]	2016	sulfuric acid; nitric acid; acetic acid at 120°C; under 3000.3 Torr; for 0.0125h; Temperature; Pressure;	88.6
QILU UNIVERSITY OF TECHNOLOGY - CN106167456 [45]	2016	nitric acid; acetic acid at 60°C	66.4
QILU UNIVERSITY OF TECHNOLOGY - CN105820086 [46]	2016	nitric acid; acetic acid at 60°C	66.4
QILU UNIVERSITY OF TECHNOLOGY - CN106349122 [47]	2017	Stage #1: salicylic acid With acetic acid Reflux; Stage #2: With nitric acid for 3h; Heating;	60
CHINA PETROLEUM CHEMICAL - CN107434768, 2017, A Location in patent: Paragraph 0016 [48]	2017	With sulfuric acid; nitric acid In chloroform at 55°C; for 0.00833333h; Temperature; Time; Solvent;	85.13
Sosič, Izidor [49]	2018	With nitric acid; acetic acid at 50°C; for 0.25h;	75
XI AN SHIYOU UNIVERSITY - CN108640936, 2018, A Location in patent: Paragraph 0012 [50]	2018	nitric acid; sodium nitrite In acetone at 45°C; for 1h;	-
Natarajan, Palani [51]	2020	3-(ethoxycarbonyl)-1-(5-methyl-5-(nitrosooxy)hexyl)pyridin-1-ium bis(trifluoromethanesulfonyl)imide at 20°C; for 2h; Ionic liquid;	89
Dolai, Anirban [52]	2023	nitric acid; acetic acid In water at 0°C;	-
Hussain, Arshad [53]	2025	nitric acid In neat (no solvent) at 70°C; for 0.07 h	74

Parallel work by Spryskow (1934) and Popow (1935) introduced sodium amalgam and nickel-catalyzed hydrogenation under elevated pressures (~12 500 Torr) [57–58], offering improved yields but still lacking control of byproduct formation. Collectively, these pioneering reports demonstrated the feasibility of nitro-to-amino transformation on functionalized aromatic acids, laying the groundwork for later refinement toward milder, selective, and environmentally compatible reductants.

A major conceptual leap occurred with Scortichini (1989), who applied electrochemical reduction in alkaline medium, marking the transition from stoichiometric metallic reagents to electronically controlled systems [61]. This innovation enabled cleaner reactions at room temperature (≈ 25 °C) and minimized inorganic residue. At the turn of the century, Sekhar & Yadav (2000) introduced microwave-assisted reduction within seconds (≈ 0.02 h) [62], drastically reducing reaction time while maintaining high conversion (~76 %). These advances reflected the growing integration of green-chemistry concepts and process intensification into synthetic methodology. Both electrochemical and microwave protocols exemplified how external energy modulation- either via current or dielectric heating- could replace hazardous reducing metals, improve atom economy, and enhance reproducibility in transforming nitroaromatics into amines under controlled aqueous or polar-solvent conditions.

From 2011 onward, several industrial patents revolutionized this conversion. MEHETA Nitesh H reported two-stage aqueous reductions operating sequentially at acidic (pH ≈ 2) and basic (pH ≈ 11.5) conditions, achieving remarkable selectivity and 91.6 % yield [63, 65]. Simultaneously, Krishnamurthy (2011) demonstrated formic-acid / Ru-complex-catalyzed hydrogenation under reflux in methanol–DMF, highlighting the potential of homogeneous metal catalysts [64]. By 2016, CELLIXBIO Private Ltd. disclosed a family of patents covering US2016/120839, US9498461, and JP2015/522549, detailing large-scale hydrogenations in water at 60 °C and 760 Torr with Na_2CO_3 buffer and precise pH (8–9.5), consistently yielding 82 % on pilot-plant scale [67–69]. These developments collectively signified the industrial validation of aqueous catalytic hydrogenation as the preferred eco-efficient route to 5-aminosalicylic acid, balancing productivity, selectivity, and environmental compliance.

Recent progress emphasizes sustainability, solid-state reactivity, and reduced energy input. KAMP Pharmaceutical (2018) introduced pressurized aqueous hydrogenations (22000–30000 Torr) achieving ~85 % yield [70], while CHANGZHOU Institute (2020) utilized mild heating at 78 °C to reach 74.7 % conversion [71].

Cutting-edge studies such as Sagmeister et al. (2021) leveraged continuous-flow H_2 systems for safe, scalable reduction [72]. Further innovations by Dewangan (2023) employed *ammonia borane* with *$NiCl_2$(dppe)* in ethanol, demonstrating chemoselective transfer hydrogenation under sealed Schlenk conditions [73]. The most recent report, Bhatnagar (2025), applied a *mechanochemical milling* approach under ~3750 Torr pressure to achieve ~71 % yield without solvents [74]. Together these advances underscore a clear evolutionary trend, from corrosive tin/sulfide reagents toward catalytic, flow, and solvent-free systems, culminating in modern sustainable technologies for 5-aminosalicylic acid production.

Outlook and Future Directions

Looking forward, the integration of solid acid supports such as sulfonated silica, zeolites, or functionalized carbon frameworks could enable recyclable heterogeneous systems with improved selectivity for nitro-group reduction under mild conditions.

Moreover, Zn-based nanocatalysts, owing to their unique surface redox behavior and biocompatibility, represent a promising alternative to conventional precious-metal catalysts, offering low toxicity and facile regeneration. Recent patented developments by Siadati et al. [75] have demonstrated the feasibility of using Zn nanoparticles dispersed on acidic solid matrices to achieve efficient, low-temperature reduction of nitroaromatics including mesalazine intermediates with exceptional turnover frequency and minimal environmental footprint, highlighting a valuable direction for future industrial-scale implementation.

Table 2. Synthesis routes from 5-nitro salicylic acid to 5-amino salicylic acid

Researcher	Year	Reagents/ condition	Yield (%)
Schmitt [54]	1864	HCl/ Tin	-
Schmitt [55]	1864	With tin; acetic acid dann verduennt man mit Wasser und faellt mit Schwefelwasserstoff;	-
Huebner [19]	1879	tin; acetic acid dann verduennt man mit Wasser und faellt mit Schwefelwasserstoff	-
Minaew [56]	1931	sodium sulfide; sodium hydroxide at 110°C;	-
Minaew [56]	1931	sodium sulfide; water at 110°C;	-
Spryskow [57]	1934	sodium hydroxide; sodium amalgam	-
Spryskow [57]	1934	sodium amalgam; sodium carbonate	-
Popow [58]	1935	water; nickel; sodium hydrogencarbonate at 100°C; under 12503.6 Torr; Hydrogenation	-
Karzew [59]	1936	sodium sulfide; sodium hydroxide at 110°C;	-
Lauer [60]	1936	Aqueous sodium sulfite	-
Scortichini [61]	1989	sodium hydroxide at 25°C; electrochemical reduction; Yield given;	-
Sekhar, K. Chandra; Yadav [62]	2000	for 0.0208333h; Reduction; microwave irradiation;	76
MEHETA NITESH H - WO2011/48535 [63]	2011	Stage 1: at 95 - 98°C; pH=2; Stage 2: With at 85 - 95°C; for 2.5h; pH=11.5 - 12; Product distribution / selectivity	91.6
Krishnamurthy [64]	2011	formic acid; [RuCl3(pHPB)3(OH2)]*2H2O In methanol; N,N-dimethyl-formamide for 18h; Reflux;	-
MEHETA NITESH H - US2012/203031 [65]	2012	G-CAT; R-CAT In water at 95 - 98°C; Product distribution / selectivity;	91.6
Hoyte [66]	2016	In for 4h; Reflux	88
CELLIXBIO PRIVATE - US2016/120839 [67]	2016	Stage 1: 5-Nitrosalicylic acid With sodium carbonate In water for 0.5h; Industrial scale; Stage 2: With hydrogen In water at 60°C; under 760.051 Torr; for 6h; pH=8 - 9.5; Industrial scale	82
CELLIXBIO PRIVATE - US9498461 [68]	2016	Stage 1: With In for 0.5h; pH=8 - 9.5; Large scale; Stage 2: In at 60°C; under 760.051 Torr; for 6h; Large scale; Stage 3: With In at 25°C; for 0.5h; Large scale	82
CELLIXBIO PRIVATE - JP2015/522549 [69]	2016	Stage #1: With In under 760.051 Torr; for 0.5h; pH=8 - 9.5; Large scale; Stage #2: With In at 60°C; for 6h; Large scale;	82
KAMP PHARMACEUTICAL - CN107778189 [70]	2018	hydrogen; sodium carbonate In water under 22502.3 - 30003 Torr; for 6h; pH=8 - 10; Heating	85
CHANGZHOU - CN111533663 [71]	2020	at 78°C; for 6h; Temperature	74.7
Sagmeister, Peter [72]	2021	H2 (g)	-
Dewangan, Chitrarekha [73]	2023	ammonia borane; nickel(II) chloride hexahydrate; 1,2-bis-(diphenylphosphino)ethane In ethanol at 100°C; Schlenk technique; Sealed tube; chemoselective reaction;	45
Bhatnagar, Samarth [74]	2025	; under 3750.38 Torr; for 6h; Milling;	71

Conclusion

The progressive development of synthetic methodologies from salicylic acid to mesalazine (5-aminosalicylic acid) reflects nearly two centuries of continuous innovation in aromatic functional-group transformations. Early researchers of the nineteenth century relied on empirical nitration and tin-based reductions with limited control and severe environmental drawbacks. Over time, systematic mechanistic understanding-especially of electronic directing effects, reagent stoichiometry, and phase behavior-enabled controlled introduction of the nitro group at the 5-position and its subsequent reduction to the amine functionality with far higher precision. The introduction of catalytic and microwave-assisted nitrations in the early 2000s dramatically increased efficiency, while patent-driven hydrogenation and aqueous catalytic processes since 2010 have transformed laboratory reactions into scalable, eco-compliant industrial routes. Recent mechanochemical and flow-hydrogenation strategies represent the latest evolution toward solvent-free, energy-efficient, and waste-minimized synthesis. These approaches not only reduce reaction times and hazards but also align with the principles of green chemistry and sustainable pharmaceutical manufacture. Overall, the historical trajectory from *acidic, metal-heavy* systems to *catalytic, recyclable, and environmentally benign* protocols exemplifies how classical organic chemistry can be re-engineered through technological and conceptual advancement. The synthesis of mesalazine today thus stands as both a model of methodological refinement and a benchmark for designing next-generation, sustainable aromatic-reduction processes in medicinal chemistry and industrial production.

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Authorship

All authors contributed to the study's conception and design, conducted the literature review, and participated in drafting and critically revising the manuscript. All authors reviewed and approved the final version for submission..

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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