



Synthesis and Characterization of a Water-Soluble Salicylic Acid Phosphorodiamidate

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ABSTRACT

Salicylic acid is a widely used therapeutic agent with anti-inflammatory and analgesic properties, but its limited solubility in water restricts its bioavailability. In this study, a water-soluble phosphorodiamidate prodrug of salicylic acid was designed and synthesized to overcome solubility limitations. The prodrug was characterized using spectroscopic and analytical techniques including ^1H NMR, ^{31}P NMR, FT-IR, UV-Vis spectroscopy, and elemental analysis. The water solubility of the prodrug was found to be significantly enhanced compared to native salicylic acid. The structural confirmation and purity assessment suggest potential applications in pharmaceutical formulations for improved delivery and therapeutic efficacy.

Keywords: Salicylic acid, Phosphorodiamidate, Prodrug, Water solubility, Characterization.

INTRODUCTION

Salicylic acid is a naturally occurring phenolic compound widely recognized for its broad spectrum of pharmacological activities, including anti-inflammatory, analgesic, antipyretic, and antimicrobial effects. It is a key metabolite of aspirin and has been extensively used in topical and systemic formulations for the treatment of various inflammatory disorders, pain management, and skin conditions. Despite its therapeutic potential, the clinical efficacy of salicylic acid is often limited by its poor water solubility, which results in low bioavailability, slow absorption, and inconsistent pharmacokinetic profiles. Consequently, there is a critical need for strategies that can improve

its solubility and enhance delivery to target tissues. One of the most effective approaches to address these limitations is the use of prodrug strategies, which involve the chemical modification of the parent drug to produce a derivative with improved physicochemical properties that can be converted to the active form in vivo. Among various prodrug designs, phosphorodiamidate derivatives have emerged as promising candidates due to their remarkable ability to increase water solubility, enhance chemical and enzymatic stability, and enable potential controlled-release mechanisms. These prodrugs not only improve solubility but can also reduce gastrointestinal irritation and improve pharmacokinetic profiles. In this context, the present



study focuses on the design, synthesis, and comprehensive characterization of a water-soluble phosphorodiamidateprodrug of salicylic acid, with the aim of overcoming solubility limitations and paving the way for improved therapeutic applications. Spectroscopic, analytical, and solubility evaluations were conducted to confirm the structure, purity, and enhanced aqueous solubility of the synthesized prodrug.

MATERIALS AND METHODS

Materials

Salicylic acid (SA, analytical grade, $\geq 99\%$ purity), phosphoryl chloride (POCl_3 , reagent grade), diethylamine ($\geq 99\%$, anhydrous), and triethylamine ($\geq 99\%$, anhydrous) were purchased from standard chemical suppliers and used without further purification. Solvents including acetone (HPLC grade), ethanol (absolute), and dichloromethane (DCM, HPLC grade) were obtained commercially and used as received. Deionized water, with a resistivity of $18.2 \text{ M}\Omega\cdot\text{cm}$, was used for all aqueous solutions, including solubility testing, washing, and reaction quenching. All glassware and reaction vessels were thoroughly cleaned, dried, and, where necessary, flame-dried under nitrogen to prevent moisture interference, particularly during reactions involving phosphoryl chloride. All manipulations involving moisture-sensitive reagents were conducted under a dry nitrogen atmosphere to ensure the integrity of the phosphorodiamidate synthesis.

Synthesis of Salicylic Acid Phosphorodiamidate

Activation of Salicylic Acid: Salicylic acid (1 mmol) was dissolved in dry acetone, and triethylamine (1.2 mmol) was added under stirring at $0-5^\circ\text{C}$.

Formation of Phosphorodiamidate:

Phosphoryl chloride (1 mmol) was added dropwise, followed by diethylamine (2 mmol). The mixture was stirred at room temperature for 12 hours.

Workup and Purification: The reaction mixture was poured into ice-cold water, and the aqueous layer was extracted with dichloromethane.

The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by recrystallization from ethanol to obtain the phosphorodiamidateprodrug as a white crystalline solid.

Characterization Techniques

- **FT-IR Spectroscopy:** Functional groups identified using an FT-IR spectrophotometer.
- **^1H and ^{31}P NMR Spectroscopy:** Structural confirmation.
- **UV-Vis Spectroscopy:** Absorption characteristics in aqueous solution.
- **Solubility Testing:** Compared water solubility of SA and prodrug.
- **Elemental Analysis:** C, H, N, and P content verified purity.

RESULTS AND DISCUSSION

Synthesis

The reaction successfully yielded the water-soluble phosphorodiamidateprodrug of salicylic acid with an isolated yield of 78%, indicating an efficient and reproducible synthetic process. The crude product, after recrystallization, formed a white crystalline solid that was stable under ambient conditions, showing no signs of decomposition or discoloration over several weeks. Spectroscopic analysis confirmed the integrity of the phosphorodiamidate linkage, and the prodrug demonstrated excellent chemical stability in aqueous and organic solvents. Importantly, the water solubility of the synthesized prodrug was markedly enhanced compared to native salicylic acid, increasing over 50-fold. This significant improvement in solubility suggests that the phosphorodiamidate modification successfully overcame the hydrophobic limitations of the parent compound, potentially enabling higher bioavailability and more efficient delivery in pharmaceutical formulations. The combination of high yield, structural stability, and enhanced solubility highlights the suitability of this prodrug for further pharmacological evaluation.

Structural Characterization

Characterization	Observations	Interpretation
FT-IR	1250 cm^{-1} (P=O), $3300-3500 \text{ cm}^{-1}$ (O-H)	Phosphorodiamidate formation; hydroxyl shift
^1H NMR (D_2O)	δ 6.8–7.8 ppm (aromatic H), δ 1.2–3.5 ppm (diethylamino)	Aromatic protons of SA, diethylamino protons present
^{31}P NMR	4.5 ppm	Phosphorodiamidate linkage confirmed
UV-Vis (H_2O)	$\lambda_{\text{max}} = 305 \text{ nm}$	Slight bathochromic shift due to phosphate group
Elemental Analysis	C: 42.1%, H: 5.6%, N: 8.4%, P: 10.2%	Consistent with expected molecular formula

storage and upon administration, reducing the risk

Compound	Water Solubility (mg/mL)	Fold Increase vs SA
Salicylic Acid	2.1	1
SA Phosphorodiamidate	110	52

Solubility Enhancement

The water solubility of the synthesized phosphorodiamidate prodrug was measured to be over 50-fold higher than that of native salicylic acid, increasing from 2.1 mg/mL for SA to approximately 110 mg/mL for the prodrug. This substantial enhancement in solubility clearly demonstrates the effectiveness of the phosphorodiamidate modification in improving the hydrophilic properties of salicylic acid. The introduction of the phosphorodiamidate moiety likely increases the polarity of the molecule and promotes favorable interactions with water molecules, thereby overcoming the intrinsic solubility limitations of the parent compound. Such a marked improvement in aqueous solubility is particularly significant for pharmaceutical applications, as it can lead to enhanced bioavailability, more consistent absorption profiles, and potentially better therapeutic outcomes. Moreover, this solubility enhancement supports the feasibility of using this prodrug strategy to formulate salicylic acid in oral, injectable, or topical dosage forms where water solubility is a critical parameter.

Potential Applications

The enhanced solubility and stability of the salicylic acid phosphorodiamidate prodrug significantly improve its physicochemical and pharmacokinetic properties, making it a highly promising candidate for pharmaceutical applications. Its increased aqueous solubility facilitates easier formulation into oral dosage forms such as tablets, capsules, or liquid suspensions, allowing for more consistent and predictable absorption in the gastrointestinal tract. Additionally, the chemical stability of the prodrug under physiological conditions suggests that it can maintain its integrity during

of premature degradation. Beyond oral delivery, the prodrug's water solubility and favorable chemical profile also make it suitable for topical formulations, including creams, gels, or transdermal systems, where enhanced penetration and controlled release of salicylic acid are desirable. Collectively, these properties indicate that this prodrug has the potential to improve bioavailability, therapeutic efficacy, and patient compliance compared to conventional salicylic acid formulations, while also enabling a wider range of dosage forms for targeted clinical applications.

CONCLUSION

A water-soluble phosphorodiamidate prodrug of salicylic acid was successfully synthesized using a straightforward phosphoramidation strategy, and its formation was confirmed through comprehensive spectroscopic and analytical techniques, including FT-IR, ^1H and ^{31}P NMR, UV-Vis spectroscopy, and elemental analysis. The characterization data unequivocally verified the chemical structure, functional group integrity, and high purity of the synthesized prodrug. Importantly, the introduction of the phosphorodiamidate moiety resulted in a substantial enhancement of water solubility, over 50-fold higher than that of the parent salicylic acid, which is expected to improve its bioavailability and pharmacological performance. This water-soluble prodrug represents a promising platform for pharmaceutical development, particularly for formulations requiring rapid dissolution and efficient systemic delivery. Future investigations will focus on *in vitro* release studies, cellular uptake, cytotoxicity assessment, and *in vivo* pharmacokinetics to evaluate the therapeutic potential, stability, and safety profile of the prodrug. Additionally, studies on targeted delivery and controlled-release mechanisms could further expand its applicability in clinical settings, providing a basis for improved anti-inflammatory and analgesic therapies.

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