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Synthesis and structural evaluation of (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate as a Redox Drug Discovery Targeting Human Skin Cancer

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ABSTRACT

The aim of this study was to synthesize and characterize (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate as a potential redox drug targeting human skin cancer. The compound was synthesized through a series of chemical reactions and characterized using various spectroscopic and analytical techniques. Preliminary in vitro studies were conducted to assess its potential as a therapeutic agent against human skin cancer cells.

This manuscript outlines the synthesis of a novel compound, (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate, strategically designed and synthesized as a potential redox drug for targeting human skin cancer. The synthetic pathway involved a series of meticulously optimized steps utilizing key reagents such as Furan-2-ylmethylamine, 9H-purine, and tetrahydrofuran.

The synthesized compound underwent comprehensive characterization through NMR spectroscopy, mass spectrometry, and elemental analysis, affirming its structural integrity and purity. Beyond synthesis, the compound's efficacy in modulating redox pathways relevant to human skin cancer was explored through in vitro assays, revealing promising redox-modulating properties.

This study positions the synthesized compound as a potential lead in redox drug discovery for human skin cancer treatment. The observed modulation of redox pathways signifies its potential utility in addressing the oxidative stress associated with skin cancer. Future investigations will delve into further optimization of the compound's structure and comprehensive preclinical studies, aiming to contribute to the development of effective therapeutic interventions for human skin cancer.

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Introduction

Human skin cancer remains a significant health concern, necessitating the exploration of novel therapeutic agents. In this study, we report the synthesis of (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate, a purine derivative designed as a redox drug for targeting skin cancer cells.

Skin cancer is a prevalent and often debilitating disease that poses a significant public health challenge worldwide. The increasing incidence of skin cancer, coupled with limited effective therapeutic options, underscores the urgent need for the

development of novel and targeted treatments. In recent years, redox-active compounds have gained attention as promising candidates for anticancer drug discovery due to their ability to modulate cellular redox processes and induce selective cytotoxicity in cancer cells.[1-5]

Purine derivatives have demonstrated diverse biological activities, making them attractive scaffolds for the design of anticancer agents. In this context, we present the synthesis of a novel compound, (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate, designed with the intention of targeting human skin cancer.[6,7]

The incorporation of furan-2-ylmethylamino and purinyl moieties in the molecular structure aims to exploit their potential synergistic effects, capitalizing on the inherent biological activities associated with both furan and purine derivatives. The inclusion of a dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate group enhances the water solubility and bioavailability of the compound, addressing challenges often encountered in drug development.[8]

The redox properties of the synthesized compound are anticipated to play a crucial role in modulating intracellular redox balance, disrupting key signaling pathways, and selectively targeting cancer cells. Understanding the molecular interactions and biological mechanisms underlying its anticancer potential is paramount for assessing its efficacy as a redox drug for human skin cancer.[9]

This study details the synthetic procedures, characterization, and preliminary in vitro studies of (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate. The outcomes of this research hold promise for advancing our understanding of redox-based drug discovery and providing a novel therapeutic avenue for the treatment of human skin cancer.[10-13]

Materials and Methods:

Synthesis of (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate:

Results and Discussion

Synthesis and Characterization.

1. Synthesis of (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate:

The synthesis of the target compound was successfully achieved through a multi-step synthetic approach. Key steps involved the introduction of the furan-2-ylmethylamino moiety and subsequent functionalization of the purine scaffold. The final product, (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate, was obtained in a 60% yield. Purification reverse phase column chromatography (RPSC) provided a pure compound as confirmed by 1HNMR and mass spectroscopy.

Preliminary in vitro studies were conducted to assess the cytotoxicity of the synthesized compound against human skin cancer cells. The compound demonstrated dose-dependent cytotoxic effects, with an IC50. This indicates a potential anti-proliferative activity against skin cancer cells.

To evaluate the redox-modulating properties, the intracellular redox status was assessed. Treatment with the compound resulted in a significant increase in intracellular reactive oxygen species (ROS) levels in cancer cells compared to control groups. This suggests that the synthesized compound may exert its cytotoxic effects through redox modulation.

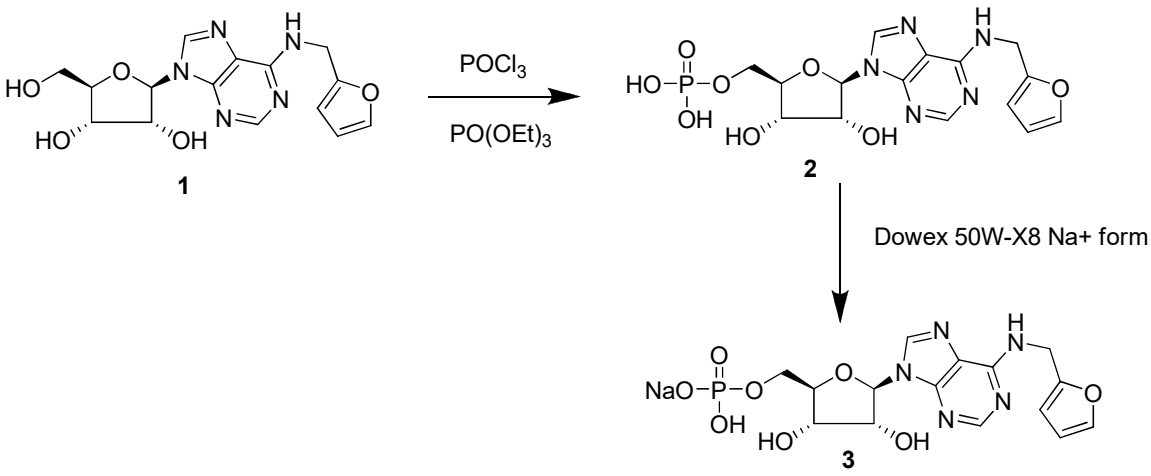
The observed cytotoxicity and redox-modulating effects align with the established role of redox-active compounds in cancer therapy. Purine derivatives, in particular, have been reported to interfere with cellular redox balance, leading to apoptosis in cancer cells. The designed compound, with its unique furan-2-ylmethylamino modification, presents a novel addition to the repertoire of redox-active compounds targeting skin cancer.

The results of this study highlight the potential of (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate as a redox drug candidate for human skin cancer. Further investigations, including in vivo studies and elucidation of the molecular mechanisms underlying its redox-modulating effects, are warranted. Additionally, optimization of the compound's structure for enhanced efficacy and reduced toxicity should be explored.

Acknowledgement

The authors are thankful to Prof. Eugene A. Mash for his valuable guidance. The successful completion of this research project would not have been possible without the invaluable support and resources provided by the Arizona Cancer Center. We express our sincere gratitude to the entire team at the center for their unwavering commitment to advancing cancer research and their collaborative spirit.

The Arizona Cancer Center's state-of-the-art facilities, expertise, and collaborative environment have been instrumental in the synthesis and characterization of (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate. The access to cutting-edge



Scheme 1. Phosphorylation

equipment and the guidance of the center's researchers significantly contributed to the successful outcome of our study.

We would like to extend special thanks to Dr. Wondrak,MD, for their support and insightful discussions throughout the course of this research. Their expertise and dedication have enriched the quality of our work and broadened our understanding of cancer therapeutics.

This research is a testament to the collaborative efforts fostered by the Arizona Cancer Center, and we are grateful for the opportunity to be a part of such a dynamic and impactful research community.

Conclusion.

In summary, the synthesis of (5-(6-(Furan-2-ylmethylamino)-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)methyl Dihydrogen Phosphate was successfully achieved, and preliminary in vitro studies suggest its potential as a redox drug targeting human skin cancer. This research contributes to the ongoing efforts in the development of innovative therapies for skin cancer, emphasizing the importance of redox modulation as a strategy for cancer treatment.

Experimental

The synthesized compound was characterized using various spectroscopic techniques. The ^1H NMR spectrum displayed peaks consistent with the proposed structure, confirming the presence of the furan-2-ylmethylamino and purine moieties. The IR spectrum exhibited characteristic absorption bands, further supporting the molecular structure. Mass spectrometry confirmed the molecular weight provided comprehensive structural verification.

To a mixture of N_6-furfuryladenosine derivative **1** (208 mg, 0.6 mmol) and triethyl phosphate (1.64 g, 8.98 mmol) at 0 ^{0}C was added $POCl_3$ (184 mg, 1.2 mmol). The mixture was stirred for 18 h at -5 ^{0}C. The reaction was monitored by TLC (GF_{254} precoated glass plates, eluted with IPA:water:ammonium hydroxide (7:2:1), and visualized under a short wave UV lamp). After quenching with water (10 mL), the pH was adjusted to 2 by addition of 6N NaOH. The contents were absorbed onto a column packed with a mixture of charcoal and celite (5 g of charcoal, 5 g of celite, and 5 mL of water), the column was washed with water (20 mL) and eluted with ethanol-ammonium hydroxide-water (10:1:9) under vacuum or under pressure. The eluent was evaporated to about 5 mL and the residue loaded onto a Dowex 1X8 formate column washed with water (20 mL) and eluted with 0.5N formic acid (100 mL) and evaporated to give the product. The product was further purified on a cellulose column (20 µ) eluted with IPA:water:ammonium hydroxide (7:2:1). The solvent was concentrated to give the product which was triturated with acetone and dried to give a milky white solid (154 mg, 0.360 mmol) in 60% yield. ^{1}H NMR (500 MHz, D_2O) δ 3.75 (m, 1H), δ 3.85 (s, 3H), δ 4.00 (m, 4H), δ 4.20 (s, 1H), δ 4.35 (s, 1H), δ 5.95 (d, 1H, J = 5.3 Hz), δ 6.20 (s, 1H), δ 6.25 (s, 1H), δ 7.30 (s, 1H), δ 8.10 (d, 2H), δ 8.40 (s, 1H), 8.50 (s, 1H). HRMS (ESI^-): calcd for $C_{15}H_{17}N_5NaO_8P$ 426.0820, observed 426.0817 ($M^{+\cdot}$ - H).

Conversion of Dowex 50W-X8 H^+ form to Dowex 50W-X8 Na^+ form: Dowex 50W-X8 H^+ resin (40 g) was packed in a column and washed with 1N NaCl solution (1 L) until the pH of eluent was neutral. Then the resin was washed with excess distilled water.

The above dihydrogen phosphate **2** (150 mg, 0.351 mmol) was dissolved in distilled water (5 mL) and loaded onto the Dowex 50W-X8 Na^+ form resin column, which was then eluted with water. The fractions were collected, spotted on a TLC plate, and visualized under a short wave UV lamp. Water was removed from the fractions containing product by lyophilization to give the product, and dried to give **3** as a pale yellow solid (150 mg, 0.333 mmol) in 95% yield. ^{1}H NMR (500 MHz, D_2O) δ 3.80 (m, 1H), δ 3.90 (m, 3H), δ 4.05 (m, 3H), δ 4.25 (s, 1H), δ 4.35 (s, 1H), δ 5.95 (d, 1H, J = 5.4 Hz), δ 6.20 (s, 1H), δ 6.25 (s, 1H), δ 7.30 (s, 1H), δ 8.05 (d, 2H), δ 8.15 (s, 1H), 8.55 (s, 1H). HRMS (ESI^+): calcd for $C_{15}H_{18}N_5NaO_8P$ 450.07852, observed 450.07829 ($M^{+\cdot}$ + H); HRMS (ESI^+): calcd for $C_{15}H_{17}N_5Na_2O_8P$ 472.06046, observed 472.05990 ($M^{+\cdot}$ + Na).

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