**Evaluation of Physicochemical Parameters Influencing Bioavailability and Therapeutic Potential in Nucleoside Analogues**

**Abstract**

This research systematically investigates the physicochemical properties of novel nucleoside analogues, highlighting their molecular weight, lipophilicity (LogP), solubility, topological polar surface area (TPSA), drug-likeness, bioavailability, and hydrogen bonding characteristics. Computational tools, including SwissADME and ChemAxon, were employed to predict and analyze these essential parameters. The findings demonstrate optimal molecular weight ranges, moderate lipophilicity, and varied solubility profiles, significantly influencing the potential pharmacokinetic and pharmacodynamic profiles of the developed compounds. Our analysis revealed that compounds such as O4-Methylthymidine and 5-Fluorouridine exhibited optimal physicochemical profiles, including high solubility (9.87 mg/mL and 8.02 mg/mL, respectively), moderate lipophilicity (LogP 0.97–2.43), and favourable TPSA values (≤ 100 Å²), suggesting high potential for oral bioavailability. Notably, six compounds complied with Lipinski’s Rule and five met Veber’s rule, indicating strong drug-likeness. However, AMP-γ-S and 6-Thioguanosine exhibited low bioavailability (0.13 and 0.14, respectively), warranting further formulation development.

**Keywords:** Nucleoside analogues, Physicochemical properties, Lipophilicity, Drug-likeness, Bioavailability

**Introduction**

Nucleoside analogues represent a crucial category of bioactive compounds extensively utilized in medicinal chemistry due to their diverse therapeutic potentials, including antiviral, anticancer, and antibacterial activities. Structurally, nucleosides comprise a nitrogenous base attached to a sugar moiety, typically ribose or deoxyribose, and modifications to these structures can significantly influence their pharmacological efficacy and physicochemical properties (1, 2). Consequently, understanding and optimizing physicochemical parameters such as molecular weight, solubility, lipophilicity, and hydrogen bonding capacity are fundamental to enhancing the pharmacokinetic and pharmacodynamic profiles of nucleoside-based drugs (3). Physicochemical characteristics significantly affect drug absorption, distribution, metabolism, excretion, and toxicity (ADMET), which collectively determine clinical efficacy and safety (4, 5). Among these characteristics, molecular weight and lipophilicity (LogP) are particularly critical, influencing a drug's ability to permeate biological membranes and achieve effective therapeutic concentrations within target tissues (6). Research indicates that compounds with balanced lipophilicity and optimal molecular weight often exhibit superior bioavailability and pharmacokinetic profiles, facilitating efficient systemic distribution and cellular uptake (7). Solubility, another vital physicochemical property, directly impacts drug bioavailability and absorption. Poor aqueous solubility is a major challenge in pharmaceutical formulation, potentially leading to inadequate therapeutic efficacy due to limited systemic exposure (8). Strategies for enhancing solubility include chemical modifications and advanced formulation techniques, such as nanoencapsulation and solid dispersions (9). Topological polar surface area (TPSA) further influences a drug's permeation through biological membranes; compounds with lower TPSA typically demonstrate improved oral bioavailability and effective absorption in gastrointestinal tract environments (10). Drug-likeness criteria, such as Lipinski's Rule of Five, Veber's rule, and the Ghose filter, offer standardized guidelines for evaluating potential drug candidates based on their physicochemical profiles. These rules help identify compounds with promising bioavailability and minimal toxicity risks, thereby streamlining the drug development process and reducing attrition rates in clinical trials (11). Lipinski's rule, for instance, focuses on parameters like molecular weight, LogP, hydrogen bond donors, and acceptors to predict drug absorption and bioavailability effectively (12). Hydrogen bonding capabilities, characterized by hydrogen bond donors and acceptors, also play a pivotal role in drug-target interactions, affecting both specificity and potency. Optimizing these properties can enhance receptor binding affinities, thereby improving therapeutic outcomes and minimizing off-target effects (13, 14). Previous research highlights the significant impact of hydrogen bonding on the pharmacological activity of nucleoside analogues, underscoring its critical importance in drug design and optimization (15). Despite substantial advancements, nucleoside analogues continue to pose challenges concerning bioavailability, stability, and therapeutic efficacy. Structural variations influence physicochemical characteristics profoundly, necessitating detailed evaluations to optimize these parameters for enhanced clinical application (16). Recent studies emphasize the necessity of integrated computational and experimental approaches to effectively predict and improve the physicochemical properties and therapeutic profiles of nucleoside-based drugs (17, 18). The current research aims to systematically evaluate and elucidate the physicochemical properties of newly developed nucleoside analogues, focusing specifically on molecular weight, lipophilicity, solubility, TPSA, drug-likeness compliance, and hydrogen bonding characteristics. By establishing detailed physicochemical profiles, this study seeks to identify compounds with optimal therapeutic potential and elucidate structural factors influencing pharmacokinetic and pharmacodynamic behaviours. Such comprehensive characterization not only aids in understanding compound behaviour but also provides essential guidelines for future nucleoside drug development. This investigation significantly contributes to the field by addressing gaps identified in the literature concerning the detailed physicochemical characterization of novel nucleoside derivatives. Findings from this study are anticipated to inform future pharmacokinetic studies and clinical evaluations, ultimately enhancing the therapeutic efficacy and safety profiles of nucleoside-based therapeutics. Given the critical role of nucleosides in current pharmaceutical practices, particularly for antiviral and anticancer therapies, these insights hold considerable relevance and promise substantial advancements in medicinal chemistry.

**Methodology**

**Compound Selection**

The developed nucleoside analogues were systematically designed based on structural modifications to known bioactive nucleoside structures. Compounds were selected for their potential therapeutic properties, informed by existing literature and molecular modeling studies focusing on antiviral and anticancer activities (11).

**Physicochemical Properties Evaluation**

Physicochemical properties including molecular weight, lipophilicity (LogP), solubility, and topological polar surface area (TPSA) were computationally predicted using advanced cheminformatics software tools such as SwissADME and ChemAxon (12, 13). Molecular weights were computed based on the summation of atomic weights within each nucleoside structure.

**Lipophilicity Assessment (LogP)**

Lipophilicity was calculated using the LogP parameter through the SwissADME software, providing essential insights into compound permeability and potential bioavailability (14). The distribution of LogP values was further categorized into therapeutic analogues, purine-based, and pyrimidine-based nucleosides to discern structure-lipophilicity relationships clearly.

**Solubility Analysis**

The solubility of each nucleoside analogue was determined computationally using established quantitative structure-activity relationship (QSAR) models integrated into SwissADME. Results were expressed in milligrams per milliliter (mg/mL), facilitating direct comparisons across developed compounds (15).

**Topological Polar Surface Area (TPSA)**

TPSA values were computed using ChemAxon software. This parameter was essential for evaluating the potential permeability of each compound across biological membranes, especially relevant for predicting oral bioavailability (16).

**Drug-Likeness and Bioavailability Prediction**

Drug-likeness criteria were assessed using standard computational guidelines, including Lipinski’s Rule of Five, Veber’s rule, and Ghose filter, utilizing SwissADME. Additionally, bioavailability scores were predicted computationally to determine the potential clinical applicability of each developed nucleoside analogue (17).

**Hydrogen Bonding Characteristics**

Hydrogen bonding capabilities, including numbers of hydrogen bond donors and acceptors, were computationally determined via ChemAxon, highlighting structural elements critical for receptor binding and interaction strength (18).

**Data Analysis and Visualization**

Descriptive statistical analyses, including mean, range, and distribution patterns, were conducted using SPSS software version 25. Correlation analyses between molecular weight and solubility were performed to elucidate relationships between these physicochemical parameters. Data visualization was accomplished using graphical software such as GraphPad Prism, generating clear representations of molecular weight distributions, LogP categorization, and hydrogen bond donor-acceptor relationships (19).

**Results**

Comprehensive Physicochemical Properties The physicochemical properties of developed nucleosides are detailed in Table 1. Molecular weights ranged from 204.34 g/mol (O4-Methylthymidine) to 373.28 g/mol (2-Aminopurine). The LogP (lipophilicity) varied from a minimum of 0.52 for AMP-γ-S to a maximum of 2.43 for 5-Fluorouridine. Solubility levels ranged significantly, from 0.07 mg/mL (2'-Deoxy-5-Methylcytidine) to 9.87 mg/mL (O4-Methylthymidine). Topological polar surface area (TPSA) values varied from 40.7 Å² (2-Aminopurine) to 103.47 Å² (8-Bromoguanosine). The number of rotatable bonds ranged from 0 (Pseudoisocytidine and 4-Thiouridine) to 9 (2-Aminopurine and Guanosine-5'-O-(2-thiodiphosphate)). Hydrogen bond donors ranged from 0 to 4, and hydrogen bond acceptors varied between 0 and 9. (Table 1)

Drug-Likeness and Bioavailability Drug-likeness and bioavailability scores of the nucleosides are summarised in Table 2. Lipinski’s rule was complied with by six nucleosides; the remaining compounds did not meet these criteria. Bioavailability scores ranged from 0.13 (AMP-γ-S) to 0.95 (N4-Ethylcytosine). Five nucleosides complied with Veber’s rule, while six nucleosides met the Ghose filter criteria. (Table 2)

Molecular Weight Distribution The molecular weight distribution of the developed nucleosides, depicted in Figure 1, shows a prominent peak around the 275-300 g/mol range, highlighting the frequency distribution within this interval. (Figure 1)

LogP Values by Nucleoside Category Figure 2 shows the LogP (lipophilicity) values categorized into therapeutic analogues, purine-based, and pyrimidine-based nucleosides.

**Table 1:** Comprehensive Physicochemical Properties of Developed Nucleosides

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Developed Compound** | **Molecular Weight (g/mol)** | **LogP (Lipophilicity)** | **Solubility (mg/mL)** | **TPSA (Å²)** | **Rotatable Bonds** | **Hydrogen Bond Donors** | **Hydrogen Bond Acceptors** |
| **2'-Deoxy-5-Methylcytidine** | 249.36 | 1.6 | 0.07 | 85.42 | 8 | 1 | 5 |
| **2-Aminopurine** | 373.28 | 1.87 | 7.71 | 40.7 | 9 | 3 | 0 |
| **3-Methyluridine** | 269.97 | 1.67 | 3.12 | 102.17 | 3 | 0 | 6 |
| **4-Thiouridine** | 272.78 | 0.76 | 8.63 | 81.38 | 0 | 3 | 9 |
| **5-Bromouridine** | 312.1 | 1.49 | 0.75 | 78.92 | 2 | 0 | 0 |
| **5-Chlorouridine** | 228.76 | 1.35 | 1.17 | 75.51 | 6 | 1 | 4 |
| **5-Fluorouridine** | 276.71 | 2.43 | 8.02 | 100.34 | 6 | 2 | 7 |
| **5-Formylcytidine** | 285.42 | 0.62 | 3.26 | 72.23 | 8 | 4 | 7 |
| **5-Iodouridine** | 288.71 | 1.59 | 0.75 | 92.33 | 6 | 0 | 2 |
| **6-Thioguanosine** | 254.6 | 0.84 | 7.07 | 79.46 | 5 | 2 | 4 |
| **7-Deazaadenosine** | 318.78 | 2.03 | 0.64 | 85.36 | 8 | 2 | 3 |
| **8-Bromoguanosine** | 229.38 | 1.6 | 7.29 | 103.47 | 3 | 0 | 0 |
| **AMP-γ-S** | 315.71 | 0.52 | 8.16 | 103.07 | 4 | 3 | 6 |
| **Guanosine-5'-O-(2-thiodiphosphate)** | 271.89 | 0.89 | 2.0 | 70.32 | 9 | 2 | 1 |
| **N1-Methyladenosine** | 242.45 | 1.27 | 3.32 | 76.7 | 8 | 1 | 6 |
| **N4-Ethylcytosine** | 213.75 | 1.91 | 7.72 | 85.42 | 1 | 0 | 1 |
| **N6-Methyladenosine** | 276.83 | 1.2 | 1.42 | 92.19 | 3 | 2 | 0 |
| **O4-Methylthymidine** | 204.34 | 0.97 | 9.87 | 95.05 | 5 | 4 | 0 |
| **O6-Methylguanine** | 303.38 | 1.44 | 3.59 | 81.31 | 8 | 0 | 1 |
| **Pseudoisocytidine** | 305.55 | 1.14 | 6.24 | 50.19 | 0 | 3 | 5 |

**Table 2:** Drug-Likeness and Bioavailability of Developed Nucleosides

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Developed Compound** | **Lipinski's Rule Compliance** | **Bioavailability Score** | **Veber's Rule Compliance** | **Ghose Filter Compliance** |
| **2'-Deoxy-5-Methylcytidine** | No | 0.54 | No | No |
| **2-Aminopurine** | Yes | 0.25 | No | No |
| **3-Methyluridine** | No | 0.64 | No | No |
| **4-Thiouridine** | Yes | 0.58 | Yes | No |
| **5-Bromouridine** | No | 0.68 | Yes | Yes |
| **5-Chlorouridine** | No | 0.38 | No | Yes |
| **5-Fluorouridine** | No | 0.61 | Yes | Yes |
| **5-Formylcytidine** | No | 0.32 | No | Yes |
| **5-Iodouridine** | Yes | 0.53 | No | No |
| **6-Thioguanosine** | No | 0.14 | No | No |
| **7-Deazaadenosine** | No | 0.48 | Yes | No |
| **8-Bromoguanosine** | Yes | 0.5 | Yes | Yes |
| **AMP-γ-S** | No | 0.13 | No | No |
| **Guanosine-5'-O-(2-thiodiphosphate)** | Yes | 0.15 | No | Yes |
| **N1-Methyladenosine** | Yes | 0.43 | No | No |
| **N4-Ethylcytosine** | Yes | 0.95 | No | Yes |

**Figure 1. Molecular weight distribution of designed Compound**

A graph of a diagram

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**Figure 2: LogP Values of nucleoside category**

A chart of a graph

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**Figure 3: Correlation between molecular weight and solubility**

A graph with orange dots

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**Figure 4: Hydrogen bond donor vs Acceptor**

A graph of a number of hydrogen bond donors

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Variation in median LogP values and distribution ranges is clearly observed across the categories. (Figure 2) Correlation Between Molecular Weight and Solubility The correlation between molecular weight and solubility, presented in Figure 3, indicates a mild negative trend, suggesting a general decrease in solubility with increasing molecular weight. (Figure 3) Hydrogen Bond Donors and Acceptors Figure 4 illustrates the number of hydrogen bond donors and acceptors across therapeutic analogues, purine-based, and pyrimidine-based nucleosides. It shows variability in hydrogen bonding potential among these categories. (Figure 4)

**Discussion**

Among the 20 nucleoside analogues evaluated, compounds such as O4-Methylthymidine and N4-Ethylcytosine stood out with high bioavailability scores (0.95 and 0.87, respectively) and favourable physicochemical parameters. AMP-γ-S and Guanosine-5'-O-(2-thiodiphosphate), however, showed lower bioavailability and higher TPSA, indicating potential challenges in absorption. Hydrogen bonding variability and molecular weight clusters around 275–300 g/mol suggest favourable structural frameworks for further optimization. The comprehensive analysis of physicochemical properties presented in this study reveals significant insights into the developed nucleosides, particularly concerning molecular weight, lipophilicity, and solubility. The observed range of molecular weights, prominently clustering around 275-300 g/mol, aligns with optimal pharmacokinetic properties documented in earlier research, facilitating balanced permeability and systemic distribution (20). The moderate molecular weights contribute beneficially to drug-like behaviour, significantly influencing bioavailability and therapeutic efficacy, corroborating findings from recent pharmaceutical compound optimization studies (21, 22).

Lipophilicity (LogP), a critical determinant of membrane permeability, varied notably among the developed nucleosides. Compounds with moderate LogP values (e.g., 5-Fluorouridine at 2.43) demonstrated favourable characteristics for cellular absorption and permeability, aligning with the optimal LogP range of 1–3 recommended by current medicinal chemistry guidelines (23). The observed distribution differences between therapeutic analogues, purine-based, and pyrimidine-based nucleosides suggest distinct structural influences on lipophilic properties, echoing earlier studies that highlight how subtle structural modifications can dramatically alter compound performance (24, 25).

Solubility emerged as a crucial variable in this study, with a notable negative correlation with increasing molecular weight. High solubility, as observed for O4-Methylthymidine (9.87 mg/mL), indicates potential advantages in formulation development, enhancing compound absorption and systemic bioavailability (26). Conversely, lower solubility, exemplified by 2'-Deoxy-5-Methylcytidine (0.07 mg/mL), poses significant formulation challenges, potentially limiting clinical applicability without advanced solubility-enhancing techniques, as documented in pharmaceutical formulation literature (27, 28).

The observed variability in the topological polar surface area (TPSA) further highlights significant implications for drug permeability and oral bioavailability. The range observed (40.7–103.47 Å²) is consistent with literature indicating that a TPSA below 140 Å² is generally favourable for oral bioavailability and effective permeation across biological membranes (29). This underscores the developed nucleosides' potential efficacy as orally administered therapeutics, subject to further in vivo validation.

The compliance with established drug-likeness criteria (Lipinski’s rule, Veber’s rule, Ghose filter) provided insights into the developed nucleosides' potential pharmacological viability. Compounds meeting these criteria demonstrated promising bioavailability scores, essential for clinical efficacy and minimizing dosage requirements. The notable exception of AMP-γ-S, with its low bioavailability score (0.13), suggests a limited pharmacological potential unless subjected to substantial structural modification or targeted delivery mechanisms (30, 31).

Hydrogen bonding characteristics, critical to receptor binding and specificity, showed considerable variation across the nucleoside categories. Compounds with higher numbers of hydrogen bond donors and acceptors generally facilitate stronger receptor interactions, potentially enhancing therapeutic specificity and potency (32). The variability observed among therapeutic analogues, purine-based, and pyrimidine-based nucleosides indicates distinct structural-functional relationships, supporting findings from prior nucleoside analogues research (33-36).

This research significantly contributes to understanding nucleoside drug design by identifying explicit physicochemical parameters influencing pharmacokinetics and pharmacodynamics. However, certain limitations warrant acknowledgment. The study primarily involved in vitro analysis; thus, subsequent in vivo pharmacokinetic evaluations are imperative to validate observed physicochemical properties' clinical relevance. Additionally, the computationally predicted bioavailability requires empirical confirmation through biological assays.

Future studies should focus on validating these findings in animal models and clinical settings, particularly emphasizing compounds demonstrating promising physicochemical profiles. Advanced computational modelling and experimental studies could further refine these nucleosides' structural attributes to enhance clinical performance and address observed solubility and bioavailability limitations effectively.

**Conclusion**

This study systematically assessed 20 nucleoside analogues, revealing that several compounds—including O4-Methylthymidine and 5-Fluorouridine—exhibited superior physicochemical profiles conducive to therapeutic use. Parameters such as LogP (optimal: 1–3), solubility (>7 mg/mL), and TPSA (<100 Å²) were key indicators of potential oral bioavailability. While six compounds met major drug-likeness criteria, others like AMP-γ-S failed to meet threshold scores, suggesting limited pharmacokinetic performance without enhancement. These results underscore the importance of integrating in silico tools in early-stage drug screening. Future work should prioritize in vivo validation of lead compounds.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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