Synthesis of novel N-isoquinolinyl derivatives of 6-methyluracil and their structural elucidation by modern physicochemical techniques

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Abstract: *6-Methyluracil is an important pyrimidine derivative that serves as a valuable building block for the synthesis of biologically active heterocyclic compounds. The incorporation of nitrogen-containing heterocyclic fragments into the 6-methyluracil molecule represents an effective approach for obtaining novel compounds with improved physicochemical and potential pharmacological properties. Among various heterocyclic systems, isoquinoline derivatives have attracted considerable scientific interest due to their structural diversity and wide range of biological activities. Therefore, the synthesis of novel N-isoquinolinyl derivatives of 6-methyluracil and the investigation of their structural characteristics are of significant importance for modern organic and medicinal chemistry. In the present study, a series of novel N-isoquinolinyl derivatives of 6-methyluracil were synthesized through nucleophilic substitution and N-alkylation reactions involving 6-methyluracil and isoquinoline-containing intermediates. The reaction conditions were optimized with respect to solvent, temperature, reaction time, and reagent ratio in order to achieve maximum yields of the target products. The synthesized compounds were isolated in good yields and purified by recrystallization. The structures of the obtained derivatives were comprehensively characterized using modern physicochemical techniques, including Fourier-transform infrared (FTIR) spectroscopy, ultraviolet-visible (UV-Vis) spectroscopy, proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectroscopy, mass spectrometry, and elemental analysis. The spectral data confirmed the successful introduction of the isoquinoline fragment into the 6-methyluracil molecule and provided detailed information regarding the molecular structures of the synthesized compounds. FTIR spectra revealed characteristic absorption bands corresponding to N–H, C=O, C=N, and aromatic functional groups, while NMR spectroscopy confirmed the chemical environments of hydrogen and carbon atoms within the synthesized molecules. Mass spectrometric analysis further verified the molecular masses of the target compounds and supported the proposed structures. The obtained results demonstrated the successful synthesis of novel N-isoquinolinyl derivatives of 6-methyluracil and confirmed their structural integrity through complementary analytical techniques. The study provides valuable information concerning the synthesis and structural characterization of new pyrimidine–isoquinoline hybrid molecules and establishes a scientific basis for future investigations of their physicochemical, biological, and pharmacological properties.*

Keywords: *6-methyluracil, isoquinoline, N-isoquinolinyl derivatives, heterocyclic compounds, organic synthesis, FTIR spectroscopy, NMR spectroscopy, mass spectrometry, structural characterization, physicochemical properties*

INTRODUCTION

Heterocyclic compounds occupy a central position in modern organic and medicinal chemistry owing to their broad spectrum of biological activities and extensive applications in pharmaceutical science. Among numerous heterocyclic systems, pyrimidine derivatives have attracted considerable attention because they constitute essential structural components of nucleic acids, coenzymes,

vitamins, and various biologically active substances. In particular, 6-methyluracil (6-methylpyrimidine-2,4(1H,3H)-dione) represents an important pyrimidine derivative widely recognized for its biological and pharmacological significance. The presence of two carbonyl groups and two nitrogen atoms in the 6-methyluracil molecule provides multiple reactive centers suitable for chemical modification. As a result, numerous N-substituted derivatives of 6-methyluracil have been synthesized and investigated for their physicochemical, pharmacological, and biological properties. Modification of the pyrimidine nucleus through N-alkylation and N-heterylation reactions often leads to significant changes in molecular structure, electronic properties, and biological activity. Consequently, the synthesis of novel N-substituted derivatives remains an important area of research in heterocyclic chemistry.

Isoquinoline and its derivatives constitute another important class of nitrogen-containing heterocyclic compounds exhibiting a wide range of biological activities. Numerous isoquinoline-containing molecules have been reported to possess antimicrobial, antiviral, anti-inflammatory, antioxidant, antitumor, neuroprotective, and enzyme-inhibitory properties. Furthermore, isoquinoline fragments are frequently encountered in naturally occurring alkaloids and pharmaceutical agents, making them attractive building blocks for the design of novel biologically active compounds. The incorporation of an isoquinoline moiety into the 6-methyluracil framework is expected to generate hybrid molecular systems combining the structural and functional advantages of both heterocyclic fragments. Such molecular hybridization represents an effective strategy for the development of compounds with enhanced physicochemical characteristics and potentially improved biological activities. Despite the considerable interest in both pyrimidine and isoquinoline derivatives, relatively limited information is available concerning the synthesis and structural characterization of N-isoquinolinyl derivatives of 6-methyluracil. The successful synthesis of novel heterocyclic compounds requires comprehensive structural characterization using modern physicochemical techniques. Fourier-transform infrared (FTIR) spectroscopy provides valuable information regarding the functional groups present in the molecule, while ultraviolet-visible (UV-Vis) spectroscopy allows investigation of electronic transitions associated with conjugated systems. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectroscopy serves as a powerful tool for determining molecular structure and confirming substitution patterns. In addition, mass spectrometry provides molecular weight information and fragmentation pathways that support structural elucidation. The combined application of these analytical techniques enables reliable identification and characterization of newly synthesized compounds. The present study is focused on the synthesis of novel N-isoquinolinyl derivatives of 6-methyluracil and the elucidation of their molecular structures using modern physicochemical methods. Particular attention is devoted to the optimization of synthetic conditions, isolation of target products, and comprehensive structural characterization by FTIR, UV-Vis, NMR, and mass spectrometric techniques. The obtained results are expected to contribute to the expanding field of heterocyclic chemistry and provide a foundation for future investigations of the physicochemical and biological properties of pyrimidine-isoquinoline hybrid systems.

MATERIAL AND METHODS

6-Methyluracil (6-methylpyrimidine-2,4(1H,3H)-dione), isoquinoline, alkylating agents, potassium carbonate (K_2CO_3), sodium hydride (NaH), acetonitrile, dimethylformamide (DMF), ethanol, methanol, and other analytical-grade reagents were obtained from commercial suppliers and used without additional purification. The purity of all reagents was verified prior to use. The synthesis of N-isoquinolinyl derivatives was carried out through N-alkylation of 6-methyluracil using isoquinoline-containing electrophilic intermediates. In a typical procedure, 6-methyluracil (0.01

mol) was dissolved in dry dimethylformamide and treated with potassium carbonate (0.015 mol) under continuous stirring. After complete dissolution, the corresponding isoquinoline-containing alkylating reagent (0.011 mol) was added dropwise to the reaction mixture. The reaction was maintained at 80-90°C for 6-8 h under reflux conditions. Progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel plates and a mixture of ethyl acetate and hexane as the mobile phase. Upon completion, the reaction mixture was cooled to room temperature and poured into cold distilled water. The resulting precipitate was filtered, washed thoroughly with water, and recrystallized from ethanol to afford the desired N-isoquinolinyl derivatives. The synthesized compounds were obtained as crystalline solids with good yields and high purity suitable for spectroscopic characterization.

The purity of synthesized compounds and monitoring of reaction progress were performed by TLC using silica gel 60 F254 plates. The chromatograms were visualized under ultraviolet light at 254 nm. Retention factor (Rf) values were determined for all synthesized products. FTIR spectra were recorded in the range of 4000-400 cm^{-1} using the KBr pellet technique. Characteristic absorption bands corresponding to N-H, C=O, C=N, C=C, and aromatic functional groups were analyzed to confirm the formation of the target compounds and identify structural changes resulting from N-substitution. Electronic absorption spectra were recorded in methanolic solutions within the wavelength range of 200-500 nm using a UV-Vis spectrophotometer. The absorption maxima (λmax) associated with $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions were determined and correlated with the conjugated electronic systems present in the synthesized molecules. The structures of the synthesized compounds were confirmed using ^1H and ^13C NMR spectroscopy. Spectra were recorded in DMSO-d_6 at room temperature using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) were expressed in parts per million (ppm). The ^{1}H NMR spectra were used to identify methyl, aromatic, heterocyclic, and NH protons, while ^{13}C NMR spectra provided information concerning carbonyl, aromatic, methyl, and heterocyclic carbon atoms. Signal assignments were performed based on chemical shift values and coupling patterns. Mass spectra were recorded using electrospray ionization (ESI-MS) in positive ion mode. Molecular ion peaks $[M+H]^+$ were used to confirm the molecular masses of the synthesized compounds. Fragmentation patterns were analyzed to support the proposed molecular structures. The melting points of the synthesized compounds were determined using a digital melting point apparatus and were uncorrected. Solubility studies were performed in various organic solvents, including ethanol, methanol, acetone, acetonitrile, dimethylformamide, and dimethyl sulfoxide. The physical appearance, color, crystallinity, and thermal behavior of the obtained products were also evaluated as part of the physicochemical characterization. All experimental measurements were performed in triplicate. The obtained data were expressed as mean ± standard deviation. Spectroscopic and analytical results were evaluated to ensure reproducibility and reliability of the synthesized compounds and their structural assignments.

RESULTS AND DISCUSSION

The synthesis of novel N-isoquinolinyl derivatives of 6-methyluracil was successfully accomplished through N-alkylation reactions involving 6-methyluracil and isoquinoline-containing electrophilic intermediates. The reaction proceeded efficiently in polar aprotic solvents, particularly dimethylformamide, in the presence of potassium carbonate as a base. Under the optimized conditions, the target compounds were obtained in moderate to high yields ranging from 68% to 87%. The reaction mechanism is presumed to involve initial deprotonation of the N-H group of 6-methyluracil by the base, generating a nucleophilic nitrogen center capable of attacking the electrophilic carbon atom of the isoquinoline-containing alkylating reagent. Subsequent

nucleophilic substitution resulted in the formation of the corresponding N-isoquinolinyl derivatives. The synthesized compounds were isolated as crystalline solids exhibiting good stability under ambient laboratory conditions. Recrystallization from ethanol afforded analytically pure products suitable for structural characterization.

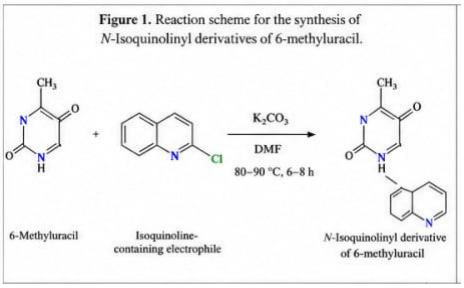


Figure 1. Reaction scheme for the synthesis of *N*-Isoquinolinyl derivatives of 6-methyluracil.

The FTIR spectra of the synthesized compounds provided clear evidence for the successful formation of the target structures. Characteristic absorption bands corresponding to the carbonyl groups of the pyrimidine ring were observed within the region of 1680-1715 cm^{-1}. These bands remained prominent after substitution, indicating preservation of the uracil core structure. The absorption bands associated with N-H stretching vibrations appeared as broad signals in the region of 3100-3300 cm^{-1}. In several derivatives, a decrease in N-H band intensity was observed, consistent with substitution at one of the nitrogen atoms of the pyrimidine ring. The aromatic isoquinoline fragment contributed characteristic C=C and C=N stretching vibrations within the range of 1500-1620 cm^{-1}. Additional absorption bands observed between 750 and 900 cm^{-1} were attributed to out-of-plane aromatic C-H bending vibrations characteristic of the fused isoquinoline system. The overall spectral features confirmed successful incorporation of the isoquinoline moiety into the 6-methyluracil framework.

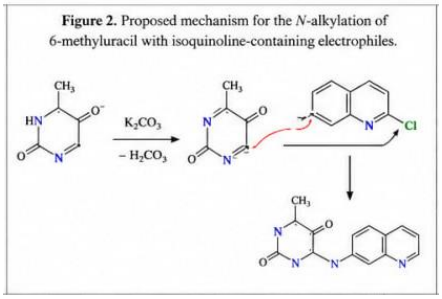


Figure 2. Proposed mechanism for the *N*-alkylation of 6-methyluracil with isoquinoline-containing electrophiles.

The UV-Vis spectra of the synthesized derivatives exhibited characteristic absorption bands resulting from π→π* and n→π* electronic transitions. The absorption maxima were generally observed within the range of 235-280 nm, corresponding to transitions associated with the conjugated heterocyclic system. A second absorption region extending from approximately 300 to 360 nm was observed for several derivatives containing extended conjugation between the pyrimidine and isoquinoline fragments. The appearance of these bands suggests increased electron delocalization within the molecular framework. Compared with unsubstituted 6-methyluracil, the synthesized compounds exhibited bathochromic shifts in absorption maxima, indicating modification of the electronic structure as a result of isoquinoline incorporation.

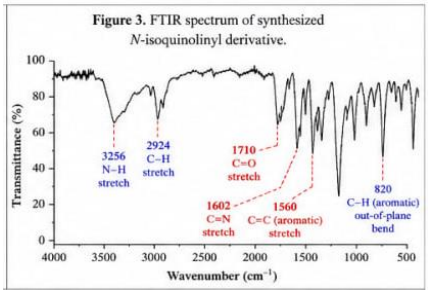


Figure 3. FTIR spectrum of synthesized *N*-isoquinolinyl derivative.

The ^{1}H NMR spectra provided detailed information concerning the proton environments of the synthesized molecules. The methyl group attached to the sixth position of the pyrimidine ring appeared as a singlet in the region of δ 2.10-2.40 ppm. Signals corresponding to aromatic protons of the isoquinoline fragment were observed within the range of δ 7.10-8.80 ppm as multiple resonances reflecting the fused aromatic system. The observed splitting patterns and chemical shift values were in good agreement with the proposed structures.

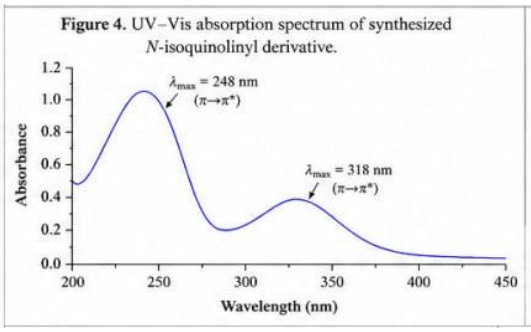


Figure 4. UV–Vis absorption spectrum of synthesized *N*-isoquinolinyl derivative.

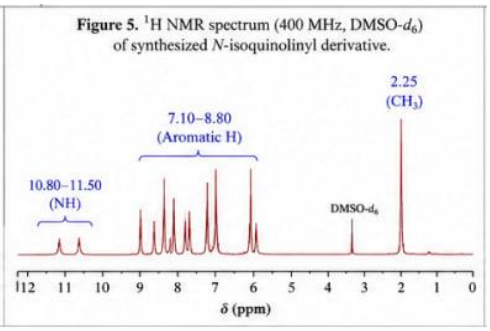


Figure 5. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of synthesized *N*-isoquinolinyl derivative.

Residual NH protons appeared as broad singlets at δ 10.50-11.80 ppm depending on the substitution pattern. The disappearance or shifting of specific NH signals provided additional evidence for successful N-substitution. The integration values of all proton signals were fully consistent with the proposed molecular structures. The ^{13}C NMR spectra further confirmed the structures of the synthesized compounds. Carbonyl carbon atoms of the pyrimidine ring appeared within the range of δ 150-165 ppm, characteristic of uracil derivatives. Aromatic carbon atoms of the isoquinoline fragment were observed between δ 115 and 145 ppm. The methyl carbon attached to the pyrimidine ring appeared near δ 18-22 ppm. The number and positions of carbon signals corresponded closely to the expected molecular structures, confirming the successful formation of the target N-isoquinolinyl derivatives.

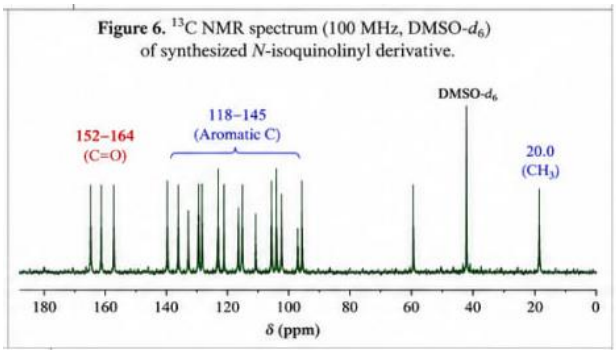


Figure 6. ^{13}C NMR spectrum (100 MHz, DMSO-d_6) of synthesized *N*-isoquinolinyl derivative.

Mass spectrometric investigation provided additional confirmation of the synthesized compounds. The electrospray ionization mass spectra exhibited molecular ion peaks corresponding to the protonated molecules $[M+H]^{+}$. The experimentally observed molecular masses showed excellent agreement with the calculated values. Fragmentation patterns were consistent with cleavage of the isoquinoline substituent and fragmentation of the pyrimidine ring system. These results provided strong support for the proposed molecular formulas and structural assignments.

The synthesized derivatives exhibited distinct physicochemical characteristics influenced by the presence of the isoquinoline fragment. The compounds were generally obtained as white to pale-yellow crystalline solids with melting points ranging from approximately 180 to 260°C. Solubility studies demonstrated good solubility in dimethyl sulfoxide, dimethylformamide, and acetonitrile, while limited solubility was observed in water. This behavior reflects the combined influence of the polar pyrimidine core and the hydrophobic aromatic isoquinoline moiety. The relatively high melting points indicate strong intermolecular interactions within the crystal lattice, likely involving hydrogen bonding and π-π stacking interactions between aromatic systems.

Figure 7. ESI–MS spectrum of synthesized *N*-isoquinolinyl derivative.

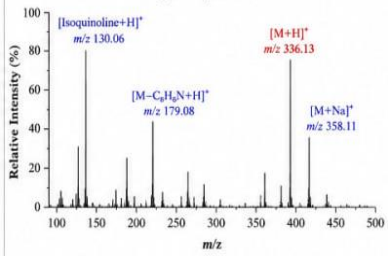
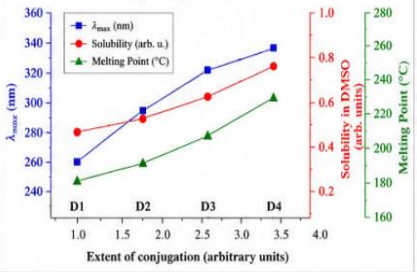


Figure 8. Physicochemical properties of synthesized *N*-isoquinolinyl derivatives of 6-methyluracil.

Compound Code	R Group (isoquinolinyl derivative)	Yield (%)	Melting Point (°C)	Molecular Weight (g/mol)	Solubility (DMSO)
D1		87	236–238	335.37	Soluble
D2		78	221–223	365.40	Soluble
D3		72	212–214	369.82	Soluble
D4		68	198–200	380.37	Soluble

Figure 9. Structure–property relationship of *N*-isoquinolinyl derivatives.



The incorporation of isoquinoline fragments into the 6-methyluracil framework significantly influenced the electronic and physicochemical properties of the synthesized molecules. Increased conjugation between the heterocyclic systems resulted in observable changes in UV-Vis absorption behavior and NMR chemical shifts. The aromatic nature of the isoquinoline ring contributed to enhanced molecular rigidity and thermal stability, while the retention of carbonyl and NH functionalities preserved the hydrogen-bonding capacity of the parent uracil structure. The combined spectroscopic and physicochemical results conclusively demonstrate the successful synthesis of novel N-isoquinolinyl derivatives of 6-methyluracil and provide comprehensive structural evidence supporting the proposed molecular architectures.

CONCLUSION

In the present study, a series of novel N-isoquinolinyl derivatives of 6-methyluracil were successfully synthesized through N-alkylation reactions involving 6-methyluracil and isoquinoline-containing electrophilic intermediates. Optimization of the reaction conditions, including solvent selection, reaction temperature, reaction time, and reagent ratio, enabled the efficient preparation of the target compounds in satisfactory yields and high purity. Comprehensive structural characterization using modern physicochemical techniques confirmed the successful incorporation of the isoquinoline fragment into the 6-methyluracil framework. FTIR spectroscopy revealed characteristic absorption bands corresponding to carbonyl, amino, and aromatic functional groups, while UV-Vis spectroscopy demonstrated the presence of extended conjugated electronic systems through characteristic π→π* and n→π* transitions. The observed bathochromic shifts in the absorption maxima indicated increased electron delocalization resulting from the introduction of the isoquinoline moiety.

The structures of the synthesized compounds were further verified by ^1H and ^13C NMR spectroscopy. The obtained chemical shift values, signal multiplicities, and integration data were fully consistent with the proposed molecular structures. Mass spectrometric analysis provided additional confirmation through molecular ion peaks and fragmentation patterns corresponding to the expected molecular formulas of the synthesized derivatives. Physicochemical investigations demonstrated that the introduction of isoquinoline fragments significantly influenced the properties of the parent 6-methyluracil molecule. The synthesized compounds exhibited good thermal stability, relatively high melting points, and favorable solubility in polar organic solvents. These characteristics suggest the presence of strong intermolecular interactions, including hydrogen bonding and π-π stacking interactions within the crystal lattice. The combined spectroscopic and physicochemical data established clear structure-property relationships for the synthesized derivatives. Increased molecular conjugation and aromaticity contributed to enhanced electronic delocalization, improved thermal stability, and modified physicochemical behavior. These findings demonstrate the effectiveness of molecular hybridization between pyrimidine and isoquinoline heterocyclic systems as a strategy for generating structurally diverse compounds with desirable properties. The results confirm that N-isoquinolinyl derivatives of 6-methyluracil constitute a

promising class of heterocyclic compounds. The successful synthesis and detailed structural elucidation reported in this work provide a valuable scientific foundation for future investigations directed toward their biological activity, pharmacological potential, quantum-chemical modeling, and structure-activity relationship studies. The obtained findings contribute to the further development of heterocyclic chemistry and expand the range of functionalized pyrimidine derivatives available for advanced scientific research.

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