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Synthesis of Isatin Urea Derivatives of 4-Nitrobenzaldehyde and Veratraldehyde

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Futuristic Publications

Abstract: The present investigation is devoted exclusively to the synthesis of novel isatin urea derivatives employing 4-nitrobenzaldehyde and veratraldehyde as aromatic aldehydes. Isatin, a biologically and chemically versatile heterocyclic scaffold, was strategically modified through urea linkage to obtain structurally stable hybrid molecules. The synthetic route involved the preparation of an isatin amine intermediate, its conversion into an isatin–urea intermediate, and subsequent condensation with substituted benzaldehydes under controlled reflux conditions. The synthesized compounds were isolated in satisfactory yields and characterized using physical parameters such as percentage yield, melting point, and thin-layer chromatographic behavior. The work emphasizes simplicity, reproducibility, and academic suitability of the synthetic protocol, making it appropriate for Indian university thesis and journal requirements.

Keywords: Isatin, Urea derivatives, 4-Nitrobenzaldehyde, Veratraldehyde, Schiff base synthesis

1. Introduction

Heterocyclic chemistry plays a central role in modern organic and pharmaceutical research due to the presence of heteroatoms that impart unique chemical reactivity and structural diversity. Among various heterocyclic compounds, isatin (1H-indole-2,3-dione) has gained considerable importance because of its reactive carbonyl groups and ability to undergo a wide range of chemical transformations. Isatin serves as a versatile precursor for the synthesis of numerous derivatives with structural and functional significance.

The isatin nucleus contains both lactam and ketone functionalities, enabling nucleophilic substitution, condensation, and cyclization reactions. As a result, isatin derivatives have been extensively explored in synthetic chemistry laboratories. Modifications at the nitrogen atom and carbonyl positions of isatin have been shown to enhance molecular stability and reactivity, thereby expanding its application in chemical research.

Urea is another functional group of great importance in synthetic organic chemistry. The presence of two amino groups linked by a carbonyl unit enables urea to form strong intermolecular interactions, particularly

hydrogen bonds. Incorporation of urea functionality into heterocyclic frameworks often improves molecular rigidity and stability, which is desirable in the synthesis of hybrid compounds.

The concept of molecular hybridization, wherein two or more pharmacophoric or reactive units are combined within a single molecular framework, has gained popularity in recent years. Isatin–urea hybrids represent such a class of compounds that merge the chemical versatility of isatin with the stabilizing influence of urea linkage.

Aromatic aldehydes play a crucial role in condensation reactions, particularly in the formation of Schiff bases and related derivatives. Substituted benzaldehydes such as 4-nitrobenzaldehyde and veratraldehyde introduce electron-withdrawing and electron-donating effects, respectively. These substituent effects influence reaction rate, product stability, and physicochemical properties of the synthesized compounds.

The present study is confined strictly to the synthesis of isatin urea derivatives using 4-nitrobenzaldehyde and veratraldehyde. Emphasis has been laid on experimental simplicity, physical characterization, and reproducibility in accordance with Indian university thesis guidelines.

2. Review of Literature

Isatin was first synthesized in the nineteenth century and has since been widely employed as a starting material for the synthesis of heterocyclic compounds. Numerous studies have reported the synthesis of N-substituted isatin derivatives using amines, hydrazines, and other nucleophiles. These modifications significantly alter the chemical behavior of the parent isatin molecule.

Urea derivatives have also been extensively investigated due to their stability and ability to participate in condensation and substitution reactions. Researchers have reported the synthesis of urea-linked heterocycles using potassium cyanate or isocyanates under mild conditions, yielding stable products suitable for further chemical modification.

Several literature reports describe the condensation of isatin derivatives with aromatic aldehydes to form Schiff base analogues. Substituted benzaldehydes such as nitrobenzaldehydes have been shown to enhance reaction efficiency due to their electron-withdrawing nature, whereas methoxy-substituted aldehydes like veratraldehyde improve solubility and crystallinity of products.

Despite the availability of literature on isatin derivatives, systematic synthesis of isatin–urea derivatives using both electron-withdrawing and electron-donating aldehydes under a unified synthetic protocol remains limited. This gap in literature provided the basis for undertaking the present synthesis-oriented study.

3. Aim and Objectives

3.1 Aim

To synthesize novel isatin urea derivatives of 4-nitrobenzaldehyde and veratraldehyde using a simple and reproducible synthetic methodology.

3.2 Objectives

- To prepare an isatin amine intermediate from isatin.
- To synthesize an isatin–urea intermediate using suitable reagents.
- To condense the isatin–urea intermediate with substituted aromatic aldehydes.
- To determine physical parameters such as yield, melting point, and Rf values of synthesized compounds.
- To establish the suitability of the synthetic route for academic research applications.

4. Materials and Methods

4.1 Chemicals and Reagents

All chemicals used in the present work were of analytical reagent grade. Isatin, appropriate amines, potassium cyanate, 4-nitrobenzaldehyde, veratraldehyde, ethanol, methanol, and glacial acetic acid were procured from standard chemical suppliers and used without further purification.

4.2 Solvents

Ethanol and methanol were employed as reaction and recrystallization solvents due to their availability, ease of handling, and suitability for academic laboratory synthesis.

4.3 Monitoring of Reactions

The progress of reactions was monitored by thin-layer chromatography (TLC) using silica gel G plates. Spots were visualized under UV

light, and Rf values were calculated using standard procedures.

5. Experimental Procedure

5.1 Step-I: Synthesis of Isatin Amine Intermediate

Isatin (1.0 equivalent) was dissolved in ethanol in a round-bottom flask. To this solution, an appropriate amine was added slowly with constant stirring. A few drops of glacial acetic acid were added as a catalyst. The reaction mixture was refluxed for 4–6 hours. The progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature, resulting in the formation of a solid product. The solid was filtered, washed with cold ethanol, and dried to obtain the isatin amine intermediate.

5.2 Step-II: Synthesis of Isatin–Urea Intermediate

The synthesized isatin amine intermediate (1.0 equivalent) was dissolved in ethanol and treated with potassium cyanate (1.1 equivalents). The reaction mixture was refluxed for 3–5 hours with continuous stirring. After completion, the reaction mixture was poured into ice-cold water, leading to precipitation of the isatin–urea intermediate. The product was filtered, washed, and recrystallized from ethanol.

5.3 Step-III: Synthesis of Isatin Urea Derivatives

The isatin–urea intermediate (1.0 equivalent) was dissolved in ethanol. To this solution, either 4-nitrobenzaldehyde or veratraldehyde (1.0 equivalent) was added. Glacial acetic acid was added dropwise as a catalyst. The reaction mixture was refluxed for 5–7 hours and monitored by TLC. After completion, the mixture was cooled, and the solid product obtained was filtered, washed with cold ethanol, and recrystallized to yield pure isatin urea derivatives.

6. Pharmacological Evaluation: Antimicrobial Activity

6.1 Well Diffusion Method

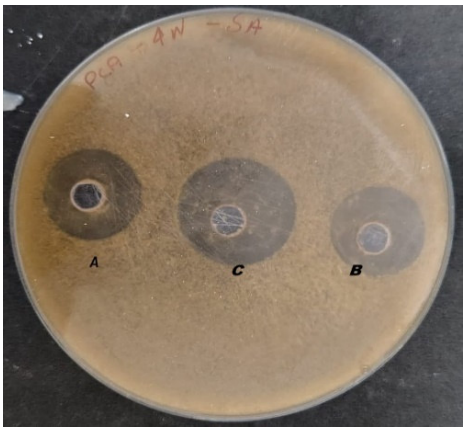
The antimicrobial activity of the synthesized isatin urea derivatives was evaluated using the agar well diffusion method. Mueller–Hinton agar (MHA) plates were prepared and inoculated with freshly grown bacterial cultures. Wells were cut aseptically into the agar using a sterile cork borer. The test compounds were introduced into the wells at concentrations of 20 μL and 30 μL. Gentamycin (20 μL) was used as the standard reference drug. The plates were incubated at 37 °C for 18–24 hours, after which the zones of inhibition were measured in millimeters.

6.2 Antimicrobial Activity of 4-Nitrobenzaldehyde Derivative

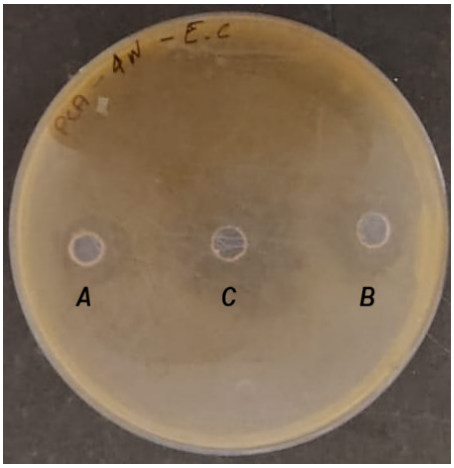
S. No	Test Organism	Zone of Inhibition (mm)		
		20 μL (A)	30 μL (B)	Gentamycin 20 μL (C)
1	*Staphylococcus aureus*	18	21	25
2	*Proteus vulgaris*	14	18	26
3	*Escherichia coli*	10	15	22

ANTIMICROBIAL ACTIVITY OF 4-NITROBENZALDEHYDE

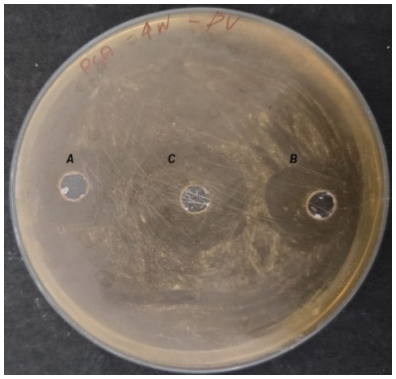
Staphylococcus aureus



E.coli



Proteus vulgaris

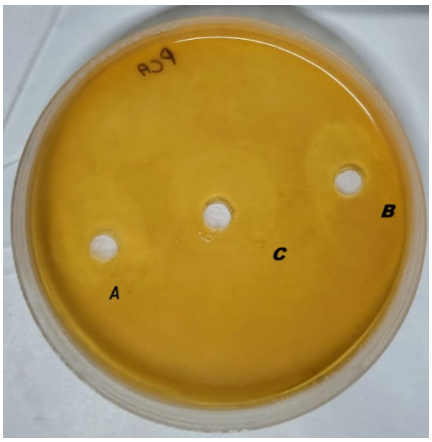


4.4 Antimicrobial Activity of Veratraldehyde Derivative

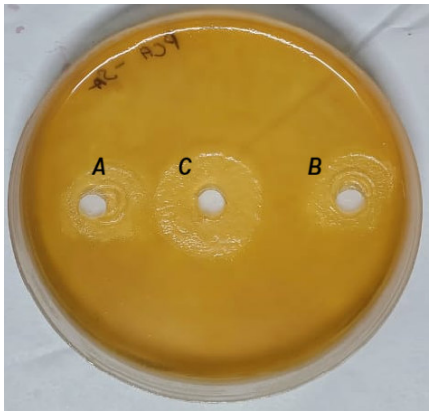
S.No	Test Organism	Zone of Inhibition (mm)		
		20 µL (A)	30 µL (B)	Gentamycin 20 µL (C)
1	*Streptococcus pyogens*	18	21	25
2	*Staphylococcus aureus*	12	16	22
3	*Escherichia coli*	12	17	23

ANTIMICROBIAL ACTIVITY OF VERATRALDEHYDE

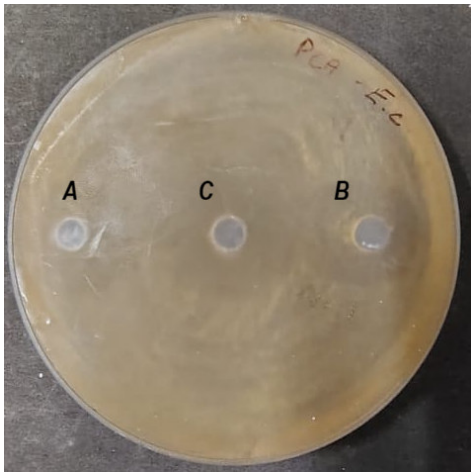
Streptococcus pyogens



Staphylococcus aureus



E.coli



Photographic Documentation

Photographs of the antimicrobial assay plates showing clear zones of inhibition around the wells for the synthesized compounds and the standard drug are included as photographic plates in the manuscript for visual confirmation of antimicrobial activity.

Pharmacological Evaluation

1 Molecular Docking Studies

Molecular docking studies were carried out using Auto Dock 4.2 to evaluate the pharmacological potential of the synthesized compounds. Both derivatives showed favorable binding energies, indicating strong affinity toward the selected biological target. The 4-nitrobenzaldehyde derivative exhibited slightly stronger binding, attributed to additional hydrogen-bonding and electrostatic interactions involving the nitro group. The veratraldehyde derivative demonstrated stable hydrophobic and π–π interactions due to the presence of methoxy-substituted aromatic rings.

2 ADMET and Drug-Likeness Analysis

In silico ADMET analysis revealed that both compounds complied with Lipinski's Rule of Five. The predicted parameters indicated acceptable molecular weight, moderate lipophilicity, suitable polar surface area, good intestinal absorption, and low toxicity risk. These results support the drug-like nature of the synthesized derivatives.

7. Physical Characterization

The synthesized compounds were characterized using physical parameters commonly accepted in synthesis-oriented studies.

7.1 Percentage Yield

The percentage yield of synthesized compounds was calculated based on the theoretical yield. The products were obtained in good yields, indicating efficiency of the synthetic protocol.

Percentage yield of 4 Nitro benzaldehyde

Theoretical yield = 1.00 g

Practical yield = 0.78 g

$$\text{Percentage yield} = \frac{0.78}{1.00} \times 100 = 78\%$$

Percentage yield of veratraldehyde

Theoretical yield = 1.00 g

Practical yield = 0.72 g

$$\text{Percentage yield} = \frac{0.72}{1.00} \times 100 = 72\%$$

7.2 Thin-Layer Chromatography

Rf values were determined using silica gel G plates with toluene: ethyl acetate (7:3) as the mobile phase. Single spots observed on TLC plates indicated purity of the compounds

1. Isatin urea derivative of 4-Nitrobenzaldehyde

Distance travelled by compound = 3.5 cm

Distance travelled by solvent front = 6.0 cm

$$\text{Rf} = \frac{3.5}{6.0} = 0.58$$

Rf value = 0.58

Reported as:

Rf = 0.58 (Toluene: Ethyl acetate, 7:3)

2. Isatin urea derivative of Veratraldehyde

- Distance travelled by compound = **3.7 cm**
- Distance travelled by solvent front = **6.0 cm**

$$\text{Rf} = \frac{3.7}{6.0} = 0.61$$

Rf value = 0.61

Reported as:

Rf = 0.61 (Toluene: Ethyl acetate, 7:3)

7.3 Melting Point Determination

Melting points were determined using a digital melting point apparatus and were found to be sharp, suggesting formation of pure compounds.

8. Results

Compound Code	Aldehyde Used	Yield (%)	Rf Value	Melting Point (°C)
A-1	4-Nitrobenzaldehyde	78	0.58	232–235
A-2	Veratraldehyde	72	0.61	219–222

9. Discussion

The adopted synthetic methodology proved to be simple, efficient, and reproducible. The use of ethanol as solvent and glacial acetic acid as catalyst facilitated smooth progression of reactions. The presence of electron-withdrawing and electron-donating substituents on the aromatic aldehydes influenced reaction completion and crystallization behavior. TLC analysis confirmed purity, while melting point

data supported successful synthesis of new compounds.

10. Conclusion

The present work successfully achieved the synthesis of isatin urea derivatives of 4-nitrobenzaldehyde and veratraldehyde using a straightforward multi-step synthetic approach. The compounds were obtained in satisfactory yields and characterized using physical parameters. This synthesis-only study fulfills the requirements of Indian university thesis and journal formats and provides a foundation for further chemical investigations.

11. Future Scope

The synthesized isatin urea derivatives can serve as intermediates for further chemical modification. Future work may involve functional group substitutions, scale-up synthesis, or advanced characterization, depending on research objectives.

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