
DESIGN, SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL SCREENING OF NOVEL ISATIN DERIVATIVES

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ABSTRACT

The present study was undertaken to synthesize, characterize, and evaluate the antibacterial activity of novel 1-benzyl isatin derivatives. The synthetic work was initiated with indoline-2,3-dione (isatin), which was subjected to N-benylation using benzyl chloride in the presence of potassium carbonate and dimethylformamide to obtain 1-benzyl indoline-2,3-dione. The synthesized intermediate was further reacted with triethyl phosphonoacetate and sodium ethoxide to produce ethyl 2-(1-benzyl-2-oxoindolin-3-ylidene)acetate. Subsequent hydrazinolysis with hydrazine hydrate yielded 2-(1-benzyl-2-oxoindolin-3-ylidene)acetohydrazide. The acetohydrazide was further reacted with salicylic acid and methyl salicylate to obtain compounds A and B, respectively. The synthesized compounds were subjected to physical characterization, including appearance, melting point, solubility, percentage yield, and thin-layer chromatography. The synthesized compounds showed melting points in the range of 127–149°C and satisfactory R_f values ranging from 0.61 to 0.75. The percentage yields of compounds 2, 3, 4, A, and B were 91.55%, 85.31%, 87.35%, 89.35%, and 91.87%, respectively. Structural confirmation was carried out using UV, FT-IR, and ¹H-NMR spectroscopy. The antibacterial activity was evaluated by the agar well diffusion method against *Staphylococcus aureus*, using ciprofloxacin as the standard drug. Compound A showed a zone of inhibition of 15 mm, while compound B showed 12 mm, compared with 30 mm for ciprofloxacin. The findings indicate that the synthesized 1-benzyl isatin derivatives were successfully prepared and structurally characterized, with compounds A and B exhibiting promising preliminary antibacterial activity.

KEYWORDS: Isatin, 1-Benzyl isatin, Acetohydrazide, Salicylic acid, Methyl salicylate, FT-IR, ¹H-NMR, Antibacterial activity, *Staphylococcus aureus*.

1. INTRODUCTION

“Chemistry is the science of molecules and their transformations. It is the science not so much of the one hundred elements but of the infinite variety of molecules that may be built from them”. Science can be viewed as a containing human effort to systematize knowledge for describing and understanding nature. That present in nature and changes in them in daily life. curd formation from milk, formation of vinegar from sugarcane juice on keeping for prolonged time and rusting of iron are some of the examples of changes which we come across many times. For the sake of convenience, science is sub-divided into various disciplines: chemistry, physics, biology, geology, etc. The branch of science that studies the preparation, properties, structure and reactions of material substances is called chemistry.

1.1 Branches Of Chemistry

- ❖ **Organic chemistry:** It is concerned with the study of most carbon based compounds.
- ❖ **Inorganic chemistry:** It deals with considered to organic, which may contain any of over 100 elements (including carbon).
- ❖ **Physical chemistry:** It deals with the application of physical laws to chemical change and chemical systems.
- ❖ **Biochemistry:** It concerned with the chemistry of life processes and living organisms.
- ❖ **Analytical chemistry:** It concerned mainly with the various techniques and laboratory methods to determine the composition of matter.

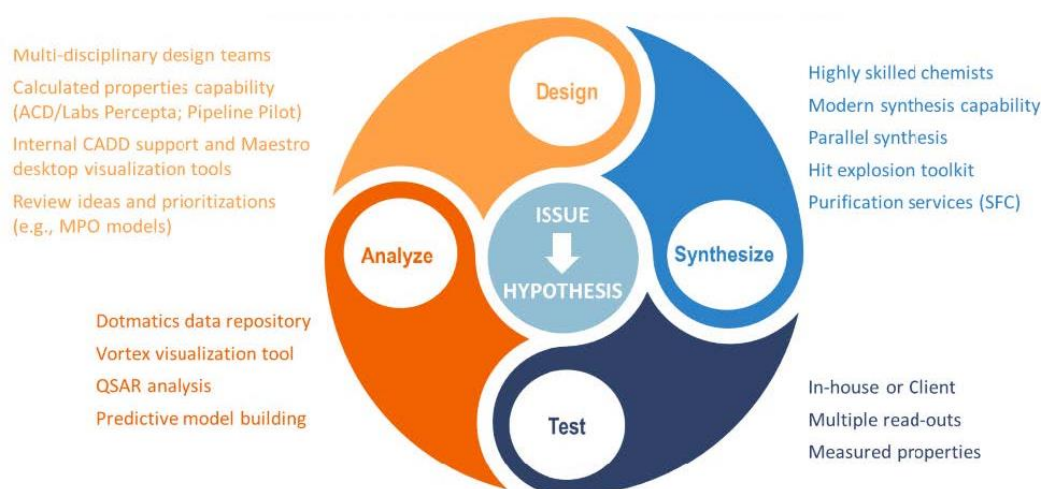


Fig: 1 Medicinal Chemistry.

1.2 Medicinal Chemistry

Medicinal Chemistry is the science that deals with the discovery or design of new therapeutic chemicals and their development into useful medicines. It may involve synthesis of new compounds, investigations of their relationships between the structure of natural or synthetic compounds and their biological activities, elucidations of their interactions with receptors of various kinds, including enzymes and DNA, the determination of their absorption, transport, and distribution properties, and studies of the metabolic transformations of these chemicals into other chemicals. Medicinal chemistry, in its crudest sense, has been practiced for several thousand years. Man has searched for cures of illnesses by chewing herbs, berries roots, and barks. Some of these early clinical trials were quite successful, however, not until the last 100 year has knowledge of the active constituents of these natural sources been known. The earliest written records of the Chinese, Indian, South American, and Mediterranean cultures described the therapeutic effects of various plant concoctions. If the approach to drug discovery continued as in ancient times, few diseases would be treatable today. Natural products make up a small percentage of drugs on the current market. Typically, when a natural product is found to be active, it is chemically modified in order to improve its properties. As a result of advances made in synthesis and separation methods and biochemical techniques since the late 1940s, a more rational approach to drug

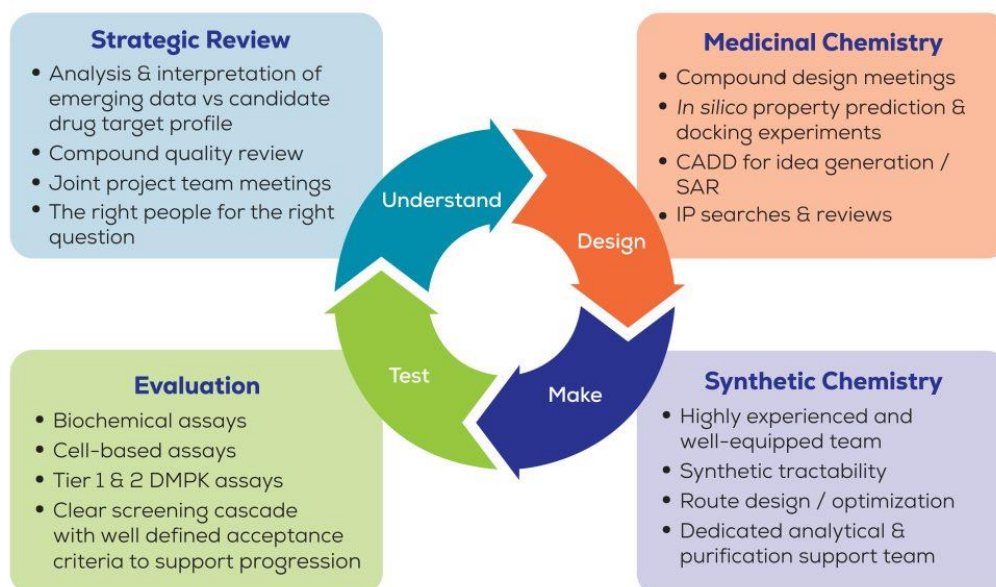


Fig: 2 Drug Design.

1.3 Isatin

Isatin (1*H*-indole-2, 3- dione) are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds, such as indole and quinoline and as raw material for drug synthesis. Isatin have also been found in mammalian tissue and their function as a modulator of biochemical processes has been the subject of several discussions. The advances in the use of isatin for organic synthesis during the last twenty-five years. (Isatin (1*H*-indole-2, 3- dione) was first discovered by Erdmann and Laurent in 1841, independently as a product from oxidation of indigo by nitric and chromic acids. Isatin (1*H*-indole-2, 3- dione) is a versatile molecule and possesses wide range of biological activities.

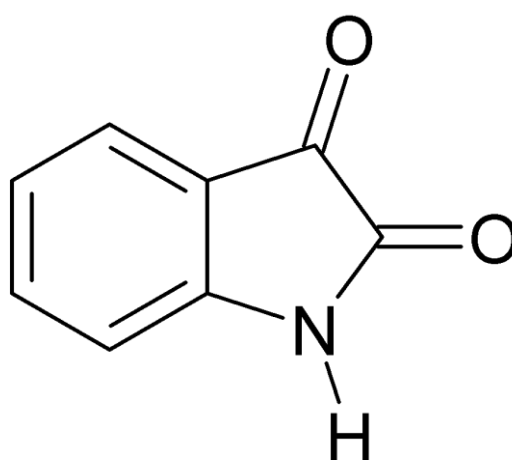


Fig: 3 Structure of Isatin.

Isatin, a heterocyclic compound, is known for its distinct chemical structure and several notable physicochemical properties. Here's an overview of its key properties:

a) Chemical Structure

- ❖ **IUPAC Name:** 1*H*-Indole-2,3-dione
- ❖ **Molecular Formula:** C₈H₇NO₂
- ❖ **Molar Mass:** 161.15 g/mol
- ❖ **Structure:** It is an indole derivative with a ketone group attached to the 2-position of the indole ring, making it an aromatic heterocycle.

b) Physical Properties

- ❖ **Appearance:** Yellow crystalline solid.
- ❖ **Melting Point:** 172–174 °C.
- ❖ **Boiling Point:** Around 400 °C (decomposes before boiling).

- ❖ **Density:** 1.33 g/cm³.
- ❖ **Solubility:** Isatin is moderately soluble in water (about 2.5 g/L), more soluble in polar solvents like ethanol, methanol, and acetone, but is generally insoluble in non-polar solvents like benzene or chloroform.
- ❖ **Odor:** Odorless or faintly aromatic.

c) Chemical Properties

- ❖ **Acidity (pKa):** The pKa values for isatin suggest that it behaves as a weak acid. This is due to the acidic nature of the NH group and the carbonyl group in the structure.

d) Spectroscopic Properties

- ❖ **UV-Vis Absorption:** Isatin shows characteristic UV absorption maxima in the range of 280–300 nm, associated with π - π^* transitions in the aromatic ring.
- ❖ **Infrared (IR):** absorption bands typically appear around: 3200–3400 cm⁻¹ (N-H stretch), 1700 cm⁻¹ (C=O stretch, carbonyl group).
- ❖ **Nuclear Magnetic Resonance (NMR):** **¹H NMR:** Peaks associated with the aromatic protons (around 7–8 ppm), along with a broad singlet for the NH group. **¹³C NMR:** Peaks around 120–140 ppm for the carbons in the aromatic ring and around 180 ppm for the carbonyl group.
- ❖ **Mass Spectrometry:** The molecular ion peak (M⁺) appears at **161 m/z**, consistent with the molecular weight of isatin.

e) Thermal Properties

- ❖ **Stability:** Isatin is relatively stable under normal conditions but can decompose when heated to high temperatures (>400 °C).
- ❖ **Decomposition:** Upon heating, isatin may decompose, releasing toxic fumes like nitrogen oxides and carbon monoxide.

f) Biological Properties

- ❖ **Pharmacology:** Isatin exhibits a variety of biological activities including antimicrobial, antiviral, anticancer, and anti-inflammatory effects. This has spurred its use in pharmaceutical research, particularly in the development of drugs targeting various conditions.
- ❖ **Toxicity:** Generally, isatin is not considered highly toxic, but as with many organic compounds, prolonged exposure or high doses could have adverse effects.

g) Synthesis

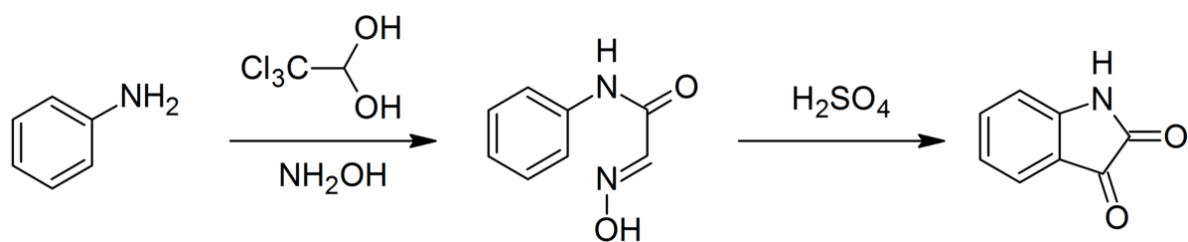


Fig: 4 Synthesis of Isatin.

2. SCHEME OF WORK

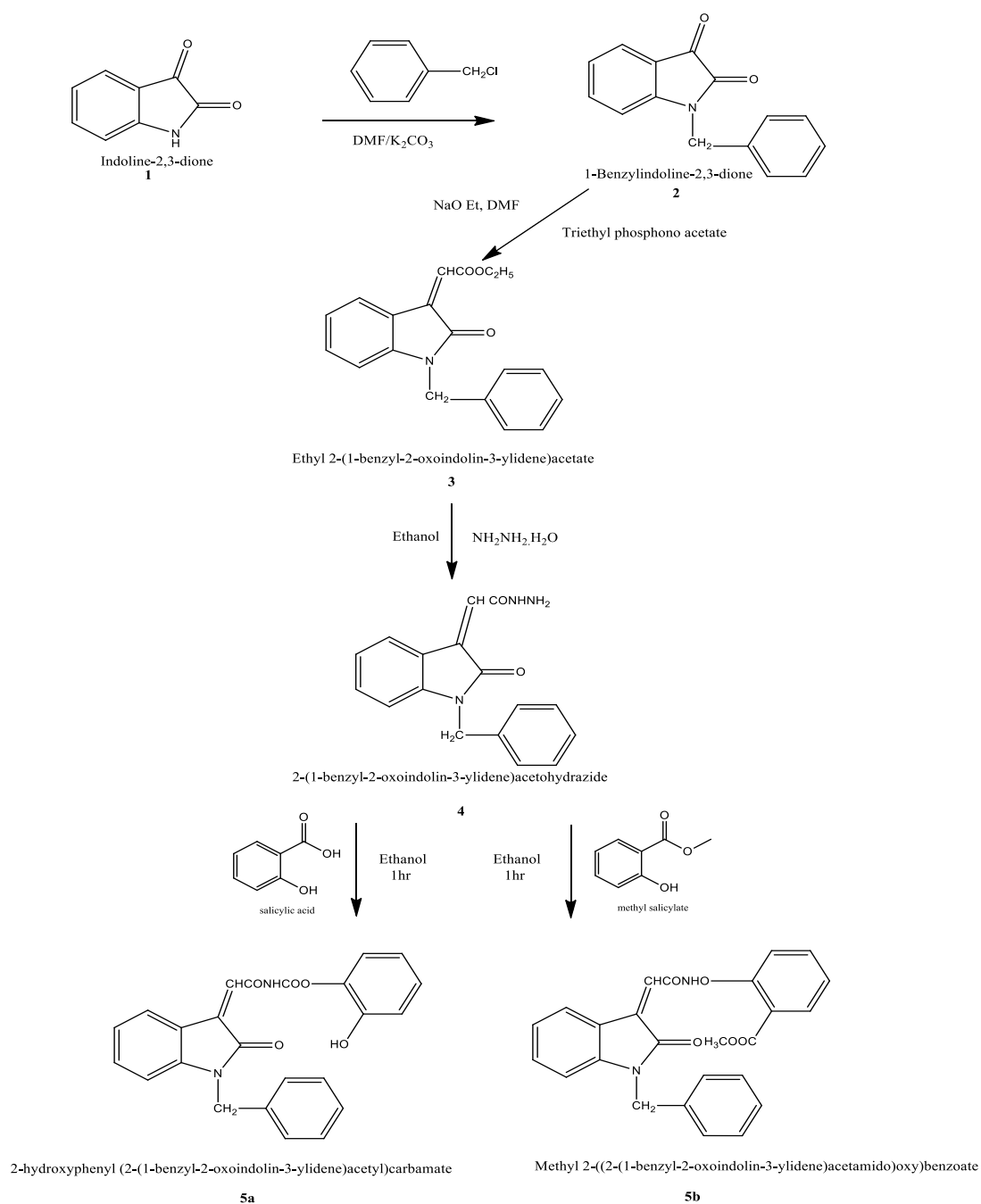
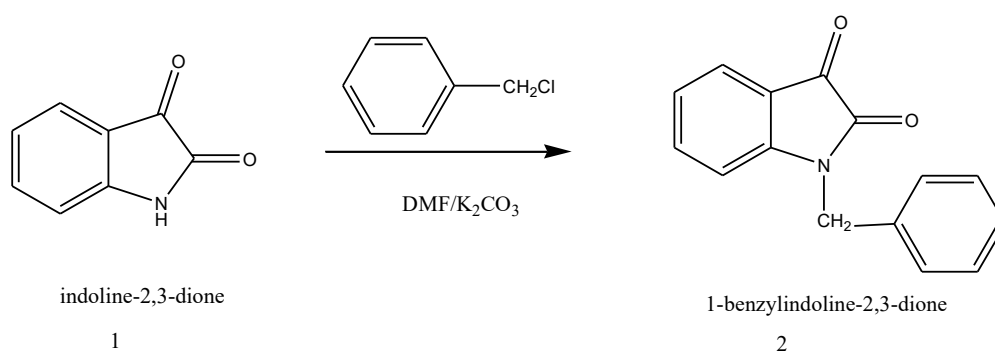


Fig: 5 Scheme of Work.

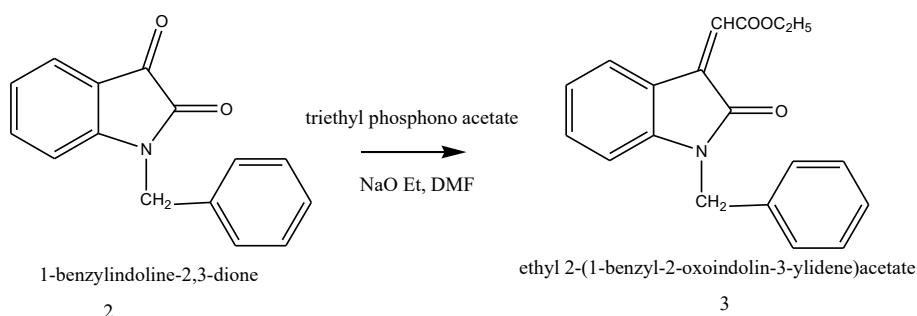
1. Method of preparation of 1-benzyl indoline-2, 3-dione from indoline- 2,3-dione (2)

In the round bottom flask take indole-2, 3-dione (isatin) 0.8 gm. (0.00337M) and equimolar quantity of benzyl chloride i.e. 6.5 ml (0.00337), mix with 20 ml of Di-methyl formamide (DMF), and this mixture add 2 gm of potassium carbonate (K_2CO_3). After gentle mixing of this reaction mixture, reflux for 2 hour, cool, and pour to 100 ml of ice cold water. The resultant orange red precipitate collected wash with water and dried and recrystallised from acetonitrile.



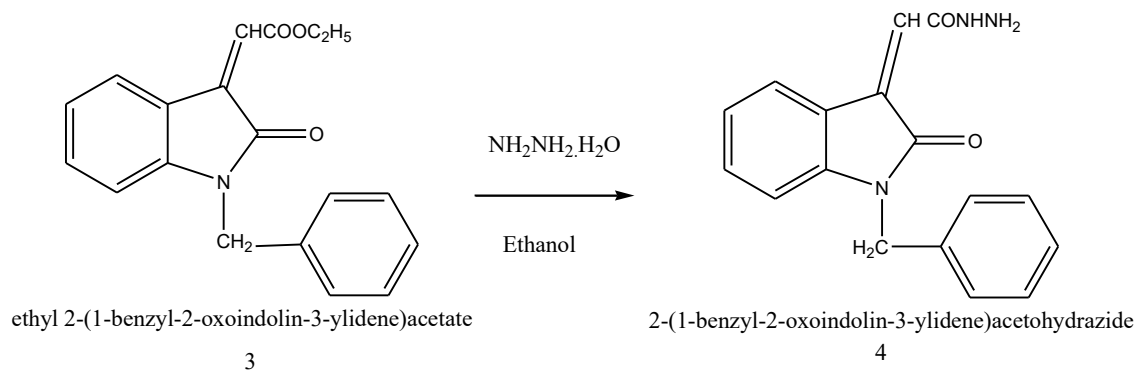
2. Synthesis of ethyl 2-(1-benzyl-2-oxoindolin-3-ylidene)acetate (3)

Equimolar quantities of 1-benzyl indoline-2, 3-dione (20 mmol), triethylphosphono acetate (20 mmol), Sodium Ethoxide (20 mmol) and in DMF (20 ml) was kept overnight at room temperature. The reaction mixture was refluxed on a steam bath for about 3 hr. It was cooled filtered recrystallized with ethanol.



3. Synthesis of 2-(1-benzyl-2-oxoindolin-3-ylidene) acetohydrazide (4)

A mixture of compound 3 (20 mmol) and hydrazine hydrate (100%; 20 mmol) in dry ethanol (40 ml) was refluxed on a steam bath for 6 hrs the excess solvent was removed under reduced pressure and the product crystallized from ethanol to obtain compound 2-(1-benzyl-2-oxoindolin-3-ylidene) acetohydrazide 4.



4. Synthesis of 2-(1-benzyl-2-oxoindolin-3-ylidene) acetohydrazide derivatives (A) & (B)

A mixture of compound 4 (30 mmol) and Salicylic acid (a), Methylsalicylate (b) in dry ethanol (40 ml) was refluxed on a steam bath for 1 hrs the excess solvent was removed under reduced pressure and the product crystallized from ethanol.

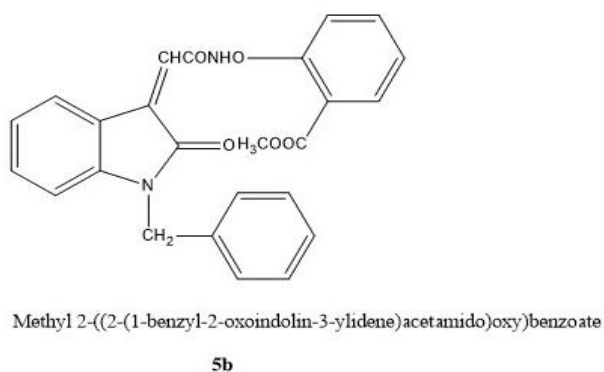
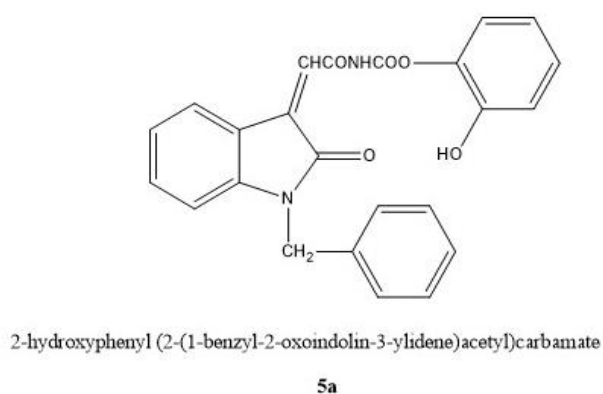


Fig: 6 Compound A & B.



Fig: 7 Compound A & B.

3. MATERIALS AND METHODS

3.1 Melting Points & Appearance

Melting points were determined using melting point apparatus and are uncorrected. The melting point physical characterization of all synthesized compounds

3.2 Solubility

At the room temperature, solubility of all synthesized compound was determined different solvent.

3.3 Thin Layer Chromatography

The purity of all synthesized compounds was monitored on TLC.

- ❖ Adsorbent used : Pre coated silica gel-G plate
- ❖ Mobile phase : Chloroform: Methanol (3:7)
- ❖ Detecting technique : Iodine chamber

3.4 Spectral Analysis

The objectives of the spectral analysis is to confirm the chemical structures of the synthesized compounds and the various functional groups in final compounds. The IR spectra of the starting compounds and intermediates were taken to confirm the changes at the reactive functional groups and then final compounds were confirmed by IR, NMR analysis.

3.5 Biological Screening

Evaluation Of Anti Bacterial Activity

The bacterial strains were sub cultured to get fresh cultures of bacteria for this purpose, a single colony from bacterial strain was inoculated on nutrient broth. The broth was incubated for 24 h at 37 °C. 14 gm of nutrient agar media was dissolved in 1 L of distilled water at PH 7 and autoclaved for 20 min at 121 °C. The media were allowed to cool down to 45 °C and poured to petri plates for preparing 75 ml of solid media. using sterile cork borer 7 wells per plate were made in the solidified media. Agar diffusion method was used for antibacterial activity. Bacterial culture was inoculated on the surface of solid media. The crude synthesized compound A and B afractions were dissolved in dimethylsulfoxide (DMSO) at the same concentration of 2 mg/ml to prepare stock solutions. from the stock solution, 1000 µl was poured into respective wells. Ciprofloxacin was used as a positive control and DMSO was used as a negative control. The zone of inhibition of crude extract and fractions were measured in mm after 24 h of incubation at 37 °C and compared with the zone of inhibition of standard drug Ciprofloxacin.

4. RESULTS AND DISCUSSION

4.1 Physical Characterization

Table: 1 Physical Characterization.

S.NO.	CODE	MOLECULAR FORMULA	MOLECULAR WEIGHT	COLOR	NATURE	PERCENTAGE YIELD
1	1	C ₈ H ₅ NO ₂	147.13	Reddish brown	Powder	-
2	2	C ₁₅ H ₁₁ NO ₂	237.25	Reddish brown	Crystal	91.55%
3	3	C ₁₉ H ₁₇ NO ₃	307.34	Orange	Crystal	85.31%
4	4	C ₁₇ H ₁₅ N ₃ O ₃	293.32	Orange	Crystal	87.35%
5	A	C ₂₄ H ₁₈ N ₂ O ₂	414.12	Orange	Crystal	89.35%
6	B	C ₂₅ H ₂₀ N ₂ O ₅	428.14	Orange	Crystal	91.87%

4.2 Physical Properties

Table: 2 Physical Properties.

CODE	MELTING POINT	RF VALUE	METHANOL	ETHANOL	CHLOROFORM	DMF	DMSO
1	145-149	0.61	+	+	+	+	+
2	127-130	0.75	+	+	+	+	+
3	145-148	0.71	+~	+~	+~	+~	+~
4	136-140	0.69	+~	+~	+~	+~	+~
A	131-135	0.71	+~	+	+~	+	+
B	136-140	0.70	+~	+	+~	+	+

Where

+ → soluble,

- → insoluble,

~+ → slightly soluble

4.3 Spectral Conformation

4.3.1 IR Spectrum Analysis

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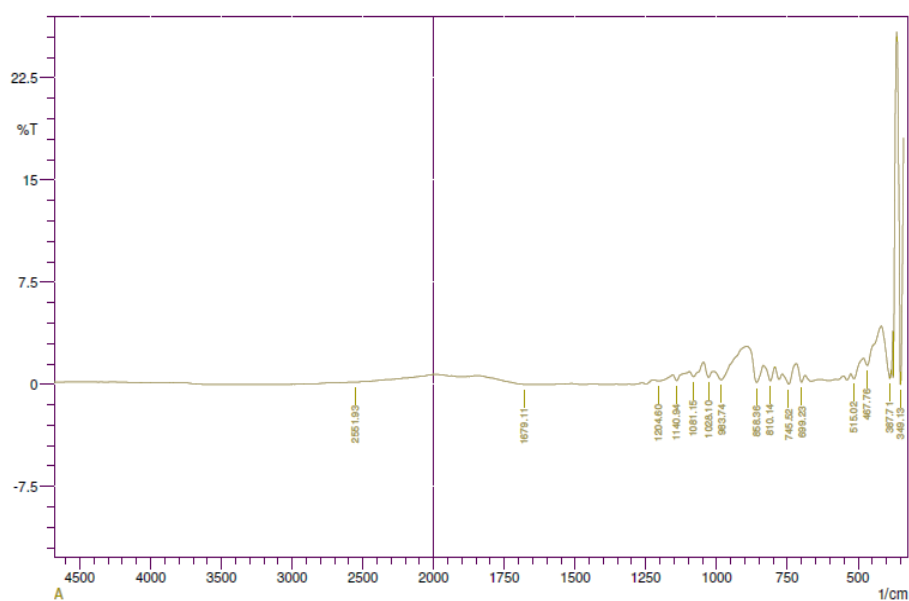


Fig: 8 IR Spectrum of Compound A.

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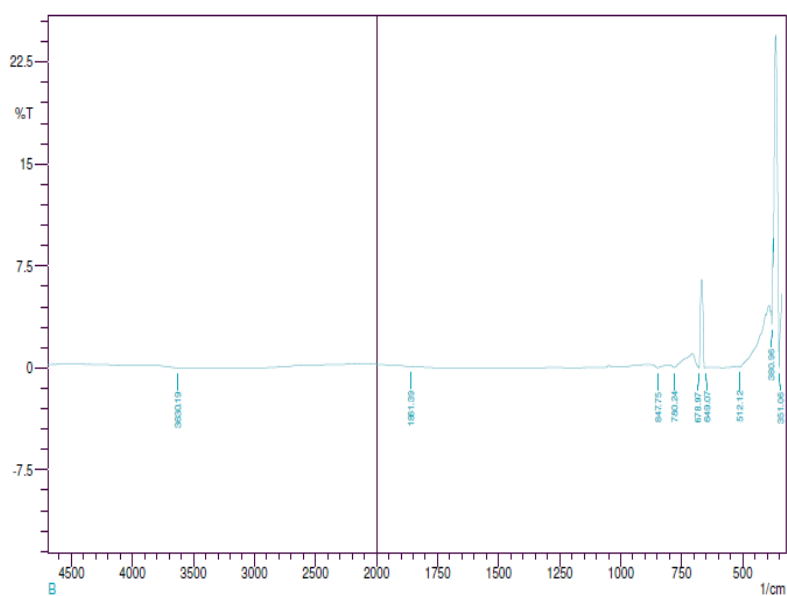


Fig: 9 IR Spectrum of Compound B.

4.3.2 ¹H NMR Spectrum Analysis

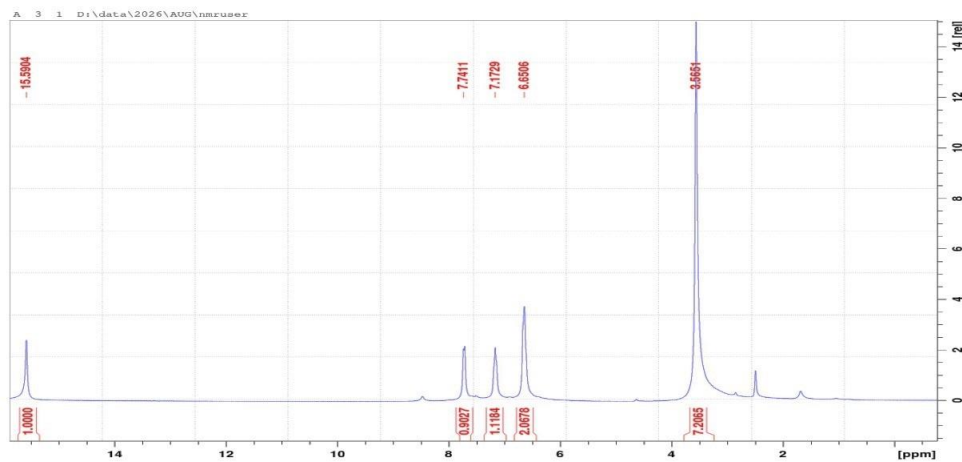


Fig: 10 NMR Spectrum of Compound A.

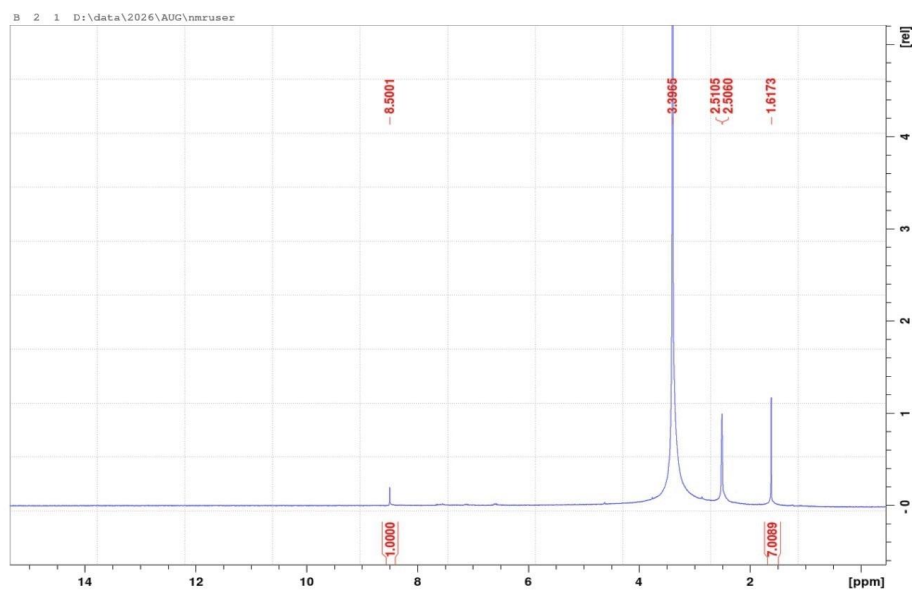


Fig: 11 NMR Spectrum of Compound B.

4.4 Biological Screening

Anti – Bacterial Activity

Table: 3 Anti – Bacterial Activity.

S.No.	Microorganisms	Control	A	B	Ciprofloxacin
		Zone of inhibition in mm			
1.	<i>Staphylococcus aureus</i>	-	15	12	30



Fig: 12 Anti – Bacterial Activity.

DISCUSSION

The present investigation focused on the synthesis and characterization of novel derivatives of indoline-2,3-dione (isatin), followed by preliminary evaluation of their antibacterial activity. Isatin was selected as the starting material because its reactive carbonyl functionality and nitrogen atom provide suitable sites for chemical modification and the development of structurally diverse derivatives.

The first synthetic step involved the N-benylation of indoline-2,3-dione using benzyl chloride in the presence of potassium carbonate and DMF. The reaction afforded 1-benzyl indoline-2,3-dione as a reddish-brown crystalline product with a percentage yield of 91.55%. The relatively high yield indicated that the N-benylation reaction proceeded efficiently under the selected conditions.

In the second step, 1-benzyl indoline-2,3-dione was reacted with triethyl phosphonoacetate in the presence of sodium ethoxide. This reaction produced ethyl 2-(1-benzyl-2-oxoindolin-3-ylidene)acetate with an 85.31% yield. The formation of this intermediate demonstrated successful incorporation of the acetate side chain into the isatin nucleus.

The ester intermediate was subsequently treated with hydrazine hydrate in ethanol to obtain 2-(1-benzyl-2-oxoindolin-3-ylidene)acetohydrazide. The compound was obtained as an orange crystalline material with a percentage yield of 87.35%. The hydrazide functional group provided an additional reactive site for further derivatization.

Further condensation reactions of the acetohydrazide with salicylic acid and methyl salicylate resulted in compounds A and B, respectively. Compound A was obtained with a yield of 89.35%, whereas compound B showed the highest yield among the final derivatives, at 91.87%. The good yields obtained for the final compounds indicate that the selected synthetic approach was suitable for producing the desired derivatives.

Physical characterization supported the successful preparation of the synthesized compounds. The melting points of the compounds ranged from 127–149°C. Variations in melting point among the derivatives may be associated with differences in molecular structure, functional groups, intermolecular interactions, and crystal packing. The synthesized compounds showed distinct colors and crystalline or powder characteristics, which provided preliminary evidence of compound formation.

TLC analysis was used to monitor the purity of the synthesized compounds. Pre-coated silica gel-G plates and chloroform:methanol were employed as the stationary and mobile phases, respectively. The R_f values ranged from 0.61 to 0.75. The appearance of distinct spots with characteristic R_f values suggested the formation of individual products and indicated satisfactory chromatographic purity.

Solubility studies showed that the synthesized compounds exhibited good solubility in several organic solvents. Compounds 1 and 2 were soluble in methanol, ethanol, chloroform, DMF, and DMSO, whereas some of the later derivatives showed slight solubility in selected solvents. Differences in solubility may be related to molecular weight, polarity, hydrogen-bonding capacity, and the presence of aromatic and heterocyclic groups.

Spectral characterization was performed to provide evidence for the proposed chemical structures. FT-IR spectroscopy was carried out using KBr pellets to identify the characteristic functional groups present in the synthesized compounds. The ^1H -NMR spectra were recorded using a 400 MHz instrument with DMSO as the solvent and tetramethylsilane as the reference. UV, FT-IR, and ^1H -NMR analyses collectively provided supporting evidence for the formation of the proposed compounds and their structural modifications.

The antibacterial activity was evaluated against *Staphylococcus aureus* using the agar well diffusion method. Compound A produced a zone of inhibition of 15 mm, while compound B produced a zone of inhibition of 12 mm. Ciprofloxacin, used as the standard antibacterial

drug, produced a zone of inhibition of 30 mm. Thus, both synthesized derivatives demonstrated antibacterial activity against *S. aureus*, although their activity was lower than that of the standard drug. Compound A showed greater antibacterial activity than compound B under the tested conditions. The difference in activity may be associated with structural variations between the two derivatives, which can influence molecular interactions with bacterial targets and penetration into bacterial cells.

Overall, the results demonstrate that systematic structural modification of the isatin nucleus can produce new derivatives with measurable antibacterial activity. The synthesized compounds showed satisfactory yields, distinct physical characteristics, acceptable TLC profiles, and spectral evidence supporting their proposed structures. The antibacterial findings provide preliminary evidence for further investigation of these compounds using additional bacterial strains, different concentrations, and quantitative antimicrobial assays.

5. CONCLUSION

The present investigation successfully demonstrated the synthesis of novel 1-benzyl isatin derivatives through a stepwise synthetic approach. The synthesized compounds were obtained in satisfactory to excellent yields, ranging from 85.31% to 91.87% for the major synthetic intermediates and final derivatives. Physical characterization, TLC analysis, and spectral studies using UV, FT-IR, and ^1H -NMR provided supporting evidence for the formation of the proposed chemical structures.

The antibacterial screening against *Staphylococcus aureus* demonstrated that both final derivatives possessed measurable antibacterial activity. Compound A exhibited a higher zone of inhibition (15 mm) than compound B (12 mm), while ciprofloxacin showed the highest activity (30 mm). These findings indicate that structural modification of the isatin nucleus can produce compounds with promising preliminary antibacterial properties.

In conclusion, the synthesized 1-benzyl isatin derivatives, particularly compound A, may serve as potential lead compounds for further antimicrobial research. However, additional studies involving different bacterial strains, minimum inhibitory concentration (MIC) determination, structure–activity relationship studies, toxicity evaluation, and in-vivo investigations are required to establish their therapeutic potential.

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