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EXPLORING THE ANTI-OXIDANT POTENCY OF NOVEL ISATIN SCHIFF BASE DERIVATIVES

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ABSTRACT

The research details the synthesis, characterization, and antioxidant evaluation of five novel Schiff base derivatives of Isatin (A1–A5). Five derivatives (A1–A5) were synthesized via condensation reactions involving Isatin, p*-phenylenediamine, and various aromatic aldehydes. Characterization was achieved through thin layer chromatography (TLC), melting point analysis, Fourier Transfer-Infrared Spectroscopy, ^{1}H-Nuclear Magnetic Resonance (NMR) and ^{13}C-Nuclear Magnetic Resonance (NMR). Using a 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay, the antioxidant activity of these derivatives was assessed. The research emphasizes that the synthesized compounds exhibited statistically significant and biologically relevant antioxidant activities. These findings highlight the importance of specific substitution patterns on the Isatin scaffold in enhancing antioxidant efficacy. The work lays a foundation for further pharmacokinetic and structure-activity relationship studies and supports the potential of these Schiff base derivatives as promising candidates in the development of multifunctional therapeutic agents.*

KEYWORDS: *Isatin, Schiff Base, Antioxidant activity.*

INTRODUCTION

Isatin (1H-indole-2,3-dione), consists of one of the most versatile scaffolds in medicinal chemistry contributing its heterocyclic nucleus to many endogenous compounds in plants and animals. This nature of Isatin permits for creation and synthesis of libraries of therapeutically relevant compounds around the basic chemical scaffold [1]. Isatin derivatives made from Schiff bases have proven to show antimicrobial action along with decent antioxidant action. Larger aromatic ring systems shows good antimicrobial and antioxidant activity. Isatin derivatives have shown evidence of greater pharmacological and medicinal activity then the parent compound. Various isatin derivatives are marketed with varied indications like Sunitinib used for cancer treatment which is a competitive tyrosine kinase inhibitor [2], Methisazone which is a mRNA inhibitor used for smallpox treatment [3], etc.

The recent generations have observed elevated levels of stress, anxiety, depression, cancer in a predominant section of population which can be attributed to having increased amounts of Reactive Oxygen Species (ROS). ROS are highly reactive chemical entities that are by-products of cellular metabolic processes. The production of ROS can also be induced through extrinsic factors such as exposure to pollution, smoke, drugs, harsh chemicals and radiations that cause irreversible changes in tissue growth and development. These unstable molecules could be superoxide anions, hydrogen peroxide, hydroxyl radical or singlet oxygen that may act as both signaling molecules or damaging agents, based on their intracellular concentration [4]. Increased levels of intracellular ROS may result in damage to DNA, lipid peroxidation, loss of structural integrity of proteins and catalytic activity of enzymes which can aid in precipitation and progression of neurodegenerative conditions like Alzheimer's disease [5],[6], cardiovascular diseases like Atherosclerosis [7] and Hypertension [8] , Type 2 Diabetes mellitus [9], Chronic Obstructive Pulmonary Disease [10],[11] and Cancer [12],[13].

To manage these pathological conditions, modern therapeutic agents aim to inculcate the idea of "one drug-multiple targets" to curb the precipitation and progression of such complex disorders by defending against oxidative injury and strengthening the body's defenses through antioxidant therapies. This would aid in reducing the formation of ROS in the body and protect the cells from damage caused by free radical. The antioxidants work by neutralizing these free radicals [9],[14].

To detect the antioxidant activity of the Isatin Schiff base derivatives in this research, a 2,2 – diphenyl-1-picrylhydrazyl (DPPH) assay is performed. The DPPH assay measures a compound's ability to scavenge free radicals, which are implicated as its efficacy in combating oxidative stress and thus assess its potential to neutralize free radicals and protect against oxidative damage. At room

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temperature, free radical DPPH (DPPH^o) transforms into a stable diamagnetic molecule, in the presence of an antioxidant (A-H) or radical species (R^o), by taking a hydrogen radical or electron, respectively, from its chemical surrounding [15].

$$DPPH^o + A\text{-}H \rightarrow DPPH\text{-}H + A^o$$
$$DPPH^o + R^o \rightarrow DPPH\text{-}R$$

At 517nm (λ_{max}), the DPPH free radical demonstrates maximum absorbance. A UV-Vis spectrophotometry is used to monitor the decrease in absorbance due the antioxidant species, at the same λ_{max}. The absorbance can be decreased by the antioxidant molecule's ability to quench free DPPH radicals, that are purple in colour, to a bleached product [16]. Apart from that, antioxidants can have indirect anti-inflammatory effects too.

Novel isatin derived hydrazone derivatives of N-amino-11-azaartemisnin had proven to show potent antioxidant activity [17]. The compound 3-(4-(3-phenylallylideneamino) phenylimino) indoline-2-one 5a gave a decent antioxidant and antimicrobial action [18]. Newer isatin-gallate hybrids had evidently shown antioxidant activity [19].

OBJECTIVE

Novel isatin derivatives have proven to show multi-targeted action with varied indications like antibacterial, anti-tubercular, antioxidant, antifungal, etc. Due to this vast medicinal activity, we had synthesized, characterized and evaluated antioxidant action of this title compounds. ROS is the major concern and to tackle this, newer highly potent antioxidant drugs need to be developed. To improve functional recovery and protect the cellular systems from eclectic sources of free radicals. Plummeting oxidative stress can lead to increased inflammation, joint pain, insulin resistance and neurodegeneration. So, to curb this oxidative stress antioxidants play a pivotal role.

EXPERIMENTAL

Materials:

SD Fine Chem Limited brand Isatin and LOBA Chem brand *p*-phenylenediamine, ethanol, glacial acetic acid and 2,3 - dichlorobenzaldehyde, Indole-3-carboxaldehyde, 2,4 - dimethoxybenzaldehyde, 3 - ethoxy - 4 - hydroxybenzaldehyde, 4 - bromobenzaldehyde were procured. SDFCL brand Ascorbic acid and LOBA Chem brand 2,2 – diphenyl-1-picrylhydrazyl (DPPH) was used. The synthesis of derivatives, product characterization and antioxidant efficacy studies were carried out in Pharmaceutical Chemistry Laboratory at Bombay College of Pharmacy.

Methodology

A reaction mixture of 0.01 moles of Isatin and 0.01 moles of *p*-phenylenediamine in 30 ml of ethanol and two to three drops of glacial acetic acid was refluxed on direct heat for an hour and cooled for two hours following filtration. The product obtained was termed Imesatin, which was used in equimolar quantity with 0.01 moles of selected aromatic aldehydes, given in Table 1, along with 30 ml ethanol and two to three drops of glacial acetic acid as reaction mixture which was refluxed on a water bath at 100°C for 8 hours and cooled at room temperature for 1-2 days following filtration to get the Isatin derivatives.

Product Identification and Characterization

The synthesized compounds (A1-A5) were identified by TLC and melting point whereas functional group identification was done by IR spectroscopy.

Thin Layer Chromatography was performed on TLC plate with 0.5 mm thick pre-coated silica gel pre-coated layer using ethyl acetate/hexane mixtures (7:3) for A3 and A4, and ethanol/hexane mixtures for A1, A2 and A5, as a mobile phase. Spots were applied using capillary tube, about 1 cm from the bottom marked by a distinct pencil line. After spotting the sample on the plate, it was allowed to dry before the plate was placed into the vapor saturated TLC chamber. When the solvent travels to the top of the plate, the plate was removed, solvent front was marked and dried. The number of the spots was detected under UV at 254 nm.

Melting point of the synthesized derivatives was determined using Thiele tube method. The compounds were packed about two to three mm height in a one-sided sealed capillary tube which was then attached to a thermometer using a thread and immersed in a liquid paraffin bath that was heated using a burner. The temperature where the solid phase converts to liquid phase is recorded as the melting point.

Fourier Transform- Infrared Spectroscopy was employed to structurally characterize the synthetic derivatives using the KBr pelleting technique to record the IR bands over a range of 400 to 4000 cm^{-1}. ^1H NMR and ^{13}C NMR was done to know the structure of the organic molecules. ^1H NMR focuses on the environment and the number of hydrogen atoms while ^{13}C NMR gives a detailed information about the types of the carbon atoms and environment. ^1H and ^{13}C NMR were performed using DMSO - d_6.

Biological Evaluation

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay was used to quantitatively assess the synthesised derivatives' in vitro antioxidant activity. A DPPH Control Solution was prepared of 0.01mM by dissolving 0.4mg of DPPH in 10 ml of DMSO.

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Solutions of the derivatives were prepared in DMSO at concentrations ranging from 10 to 100 µg/ml. 2 ml of each derivative sample solutions were transferred into ambered test tube along with 2 ml of the DPPH Control Solution, agitated vigorously and kept in the dark for 30 minutes. Similarly, a standard antioxidant solution of Ascorbic acid was prepared at the same concentration range, of which 2ml of standard solutions was added to 2 ml of DPPH Control Solutions in ambered test tubes, agitated vigorously and kept in the dark for 30 minutes. Absorbance for control, sample and standard solutions were measured at 517nm using a UV-Visible Spectrophotometer. The antioxidant activity was expressed as percent inhibition of the DPPH radical, calculated using the formula:

% Inhibition = $[(A_0-A_n) / A_0] \times 100$

Where A_0 is the control absorbance and A_n is the absorbance of the samples [16],[20].

Statistical Analysis

Statistical relevance of the results obtained through evaluation of percent inhibition in DPPH radical scavenging screening of synthesized derivatives were analyzed using Friedman's Test, a non-parametric statistical test . The statistical significance level (α) was set at 0.05.

RESULTS

Product Identification and Characterization

(3Z)-3-((4-((2,3-dichlorobenzylidene) amino) phenyl)imino)indolin-2-one (**A1**)

Yield = 84.97%, m.p. 300-320°C ; IR (cm^{-1}) : 3450 (N-H), 1741 (C=O), 1611 (C=N), 648 (C-Cl), 2922 (C-H), ^{1}H - NMR (DMSO - d_6) : 10.03 (s, 1H, N-H), 6.5 - 8.0 (m, 11H, Ar - H), 8.63 (s, 1H, N=CH), ^{13}C - NMR (DMSO - d_6) : δ 163.5 (-N=C), 129.4 (C- 4), 124.4 (C- 5), 131.2 (C - 6), 119.4 (C - 7), 141.2 (C - 8), 117.7 (C - 9), 151.7 (C - 1'), 123.6 (C - 2'),(C - 3'), (C - 5'), (C - 6'), 146.6 (C - 4'), 157.0 (N=CH), 134.8 (C - 1''), 130.8 (C - 2''), 142.7 (C - 3''), 132.5 (C - 4''), 128.3 (C - 5''), 125.3 (C - 6''), 150.1 (C=O).

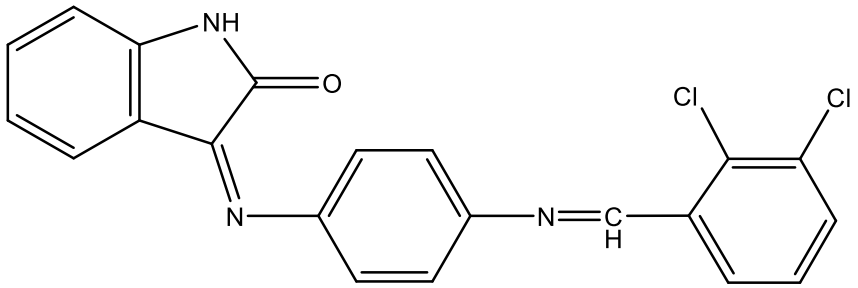


Figure 1: Chemical Structure of Derivative A1

(3Z)-3-((4-(((1H-indol-3-yl) methylene) amino) phenyl)imino)indolin-2-one (**A2**)

Yield = 48.62 %, m.p. 280-300°C ; IR (cm^{-1}) : 3728 (N-H), 1731 (C=O), 1611 (C=N), 3166 (C-H), ^{1}H - NMR (DMSO - d_6) : 10.03 (s, 1H, N-H), 11.28 (s, 1H, N-H), 6.5 - 8.5 (m, 13H, Ar - H), 9.72 (s, 1H, N=CH), ^{13}C - NMR (DMSO - d_6) : δ 163.5 (-N=C), 129.4 (C- 4), 124.4 (C- 5), 131.2 (C - 6), 119.4 (C - 7), 141.2 (C - 8), 117.7 (C - 9), 151.7 (C - 1'), 123.6 (C - 2'),(C - 3'), (C - 5'), (C - 6'), 146.6 (C - 4'), 160.0 (N=CH), 110.4 (C - 1''), 130.7 (C - 2''), 111.1 (C - 4''), 121.7 (C - 5''), 119.8 (C - 6''), 121.8 (C - 7''), 126.3 (C - 8''), 137.1 (C - 9''), 150.1 (C=O).

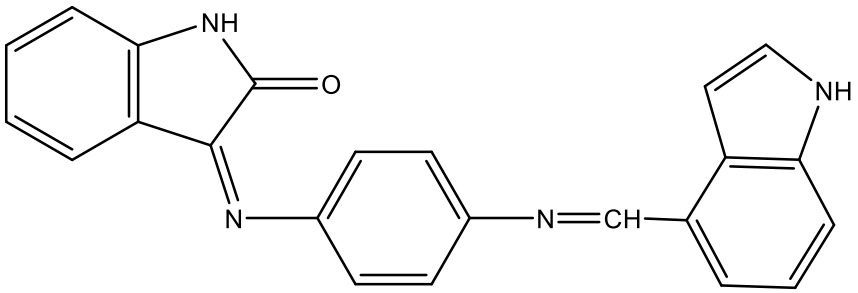


Figure 2 : Chemical Structure of Derivative A2

(3Z)-3-((4-((2,4-dimethoxybenzylidene) amino) phenyl)imino)indolin-2-one (**A3**)

Yield = 72.78%, m.p. 300-320°C ; IR (cm^{-1}) : 3460 (N-H), 1738 (C=O), 1594 (C=N), 1159 (C-O), 2973 (C-H), ^{1}H - NMR (DMSO - d_6) : 10.03 (s, 1H, N-H), 6.5 - 8.0 (m, 11H, Ar - H), 8.94 (s, 1H, N=CH), 3.84, 3.81 (s, 3H,O - CH_3), ^{13}C - NMR (DMSO - d_6) : δ 163.5 (-N=C), 129.4 (C- 4), 124.4 (C- 5), 131.2 (C - 6), 119.4 (C - 7), 141.2 (C - 8), 117.7 (C - 9), 151.7 (C - 1'), 123.6 (C - 2'),(C - 3'), (C - 5'), (C - 6'), 146.6 (C - 4'), 156.5 (N=CH), 117.2 (C - 1''), 159.5 (C - 2''), 101.5 (C - 3''), 163.9 (C - 4''), 106.7 (C - 5''),

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133.0 (C - 6”), 150.1 (C=O).

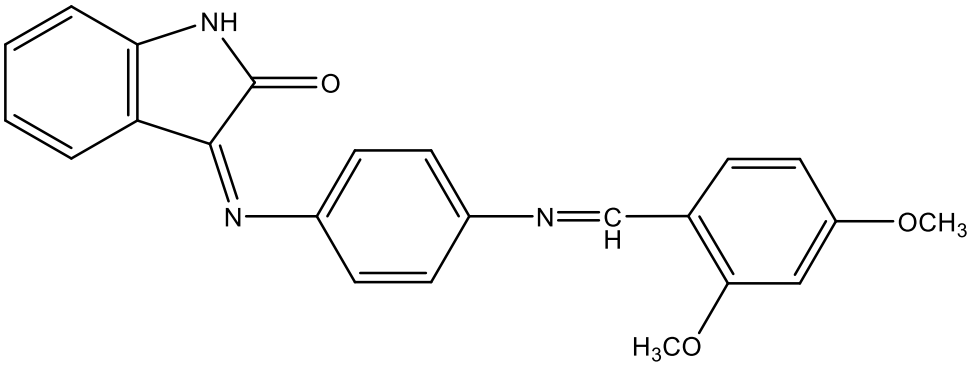


Figure 3 : Chemical Structure of Derivative A3

(3Z)-3-((4-((4-ethoxy-3-hydroxybenzylidene) amino) phenyl)imino)indolin-2-one (**A4**)
Yield = 25.97%, m.p. 310-330°C ; IR (cm^{-1}) : 3286 (N-H), 1649 (C=O), 1514 (C=N), 1147 (C-O), 3212 (C-H), ^{1}H - NMR (DMSO - d_6) : 10.03 (s, 1H, N-H), 6.5 - 8.0 (m, 11H, Ar - H), 8.52 (s, 1H, N=CH), 9.27 (s, 1H, O-H), 4.13 (q, 2H, O - CH_2), 1.42 (t, 3H, CH_3), ^{13}C - NMR (DMSO - d_6) : δ 163.5 (-N=C), 129.4 (C- 4), 124.4 (C- 5), 131.2 (C - 6), 119.4 (C - 7), 141.2 (C - 8), 117.7 (C - 9), 151.7 (C - 1’), 123.6 (C - 2’),(C - 3’), (C - 5’), (C - 6’), 146.6 (C - 4’), 160.0 (N=CH), 130.3 (C - 1”), 115.5 (C - 2”), 147.4 (C - 3”), 147.9 (C - 4”), 112.4 (C - 5”), 125.1 (C - 6”), 150.1 (C=O), 64.9 (C - 1”’), 14.8 (C - 2”’).

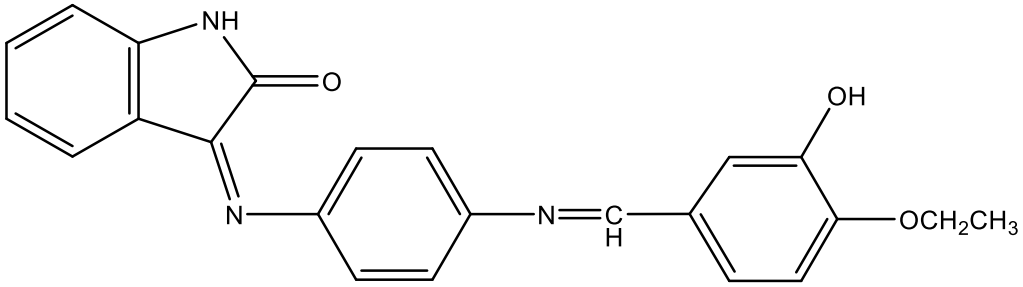


Figure 4 : Chemical Structure of Derivative A4

(3Z)-3-((4-((4-bromobenzylidene) amino) phenyl)imino)indolin-2-one (**A5**)
Yield = 85.31%, m.p. 270-290°C ; IR (cm^{-1}) : 3410 (N-H), 1726 (C=O), 1616 (C=N), 690 (C-Br), 3165 (C-H), ^{1}H - NMR (DMSO - d_6) : 10.03 (s, 1H, N-H), 6.5 - 8.0 (m, 12H, Ar - H), 8.58 (s, 1H, N=CH), ^{13}C - NMR (DMSO - d_6) : δ 163.5 (-N=C), 129.4 (C- 4), 124.4 (C- 5), 131.2 (C - 6), 119.4 (C - 7), 141.2 (C - 8), 117.7 (C - 9), 151.7 (C - 1’), 123.6 (C - 2’),(C - 3’), (C - 5’), (C - 6’), 146.6 (C - 4’), 160.0 (N=CH), 135.4 (C - 1”), 128.5 (C - 2”), 131.7 (C - 3”), 125.4 (C - 4”), 131.7 (C - 5”), 128.5 (C - 6”), 150.1 (C=O).

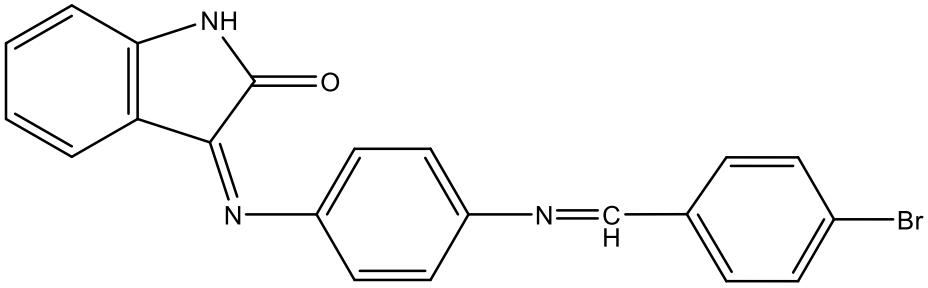


Figure 5 : Chemical Structure of Derivative A5

Anti-oxidant Activity
On analysis, it was established that compound A1 and A5 demonstrate a concentration dependent increase in antioxidant activity. Compounds A3 and A4 demonstrate a concentration dependent decrease in antioxidant activity. Compound A2 demonstrates a minimal increase in antioxidant activity with regards to its increasing concentration. The results of anti-oxidation potency of the synthesized compounds are compared with a standard anti-oxidant i.e., Ascorbic acid and represented in terms of measure of absorbance in Table 1 as well as percent inhibition in Table 2. A graphical representation of the percent inhibition against concentration for all the five synthesized derivatives in shown in Figure 6.

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Conc (mcg/ml)	Absorbance at 517 nm					
	S	A1	A2	A3	A4	A5
10	0.860	0.673	0.546	0.566	0.635	0.723
25	0.745	0.623	0.556	0.631	0.686	0.686
50	0.593	0.585	0.606	0.688	0.751	0.676
75	0.402	0.585	0.540	0.861	0.884	0.615
100	0.279	0.524	0.476	0.806	0.918	0.522
Absorbance of Control Solution, $A_0 = 1.286$						

Table 1: Free Radical Scavenging of Derivatives – Absorbance at 517nm

Conc (mcg/ml)	% Inhibition					
	S	A1	A2	A3	A4	A5
10	33.12	47.66	57.54	55.98	50.62	43.77
25	42.06	51.55	56.76	50.93	46.65	46.65
50	53.88	54.51	52.87	46.50	41.60	47.43
75	68.74	54.51	58.00	33.00	31.25	52.17
100	78.30	59.22	62.98	37.32	28.61	59.40

Table 2: Free Radical Scavenging of Derivatives - % Inhibition

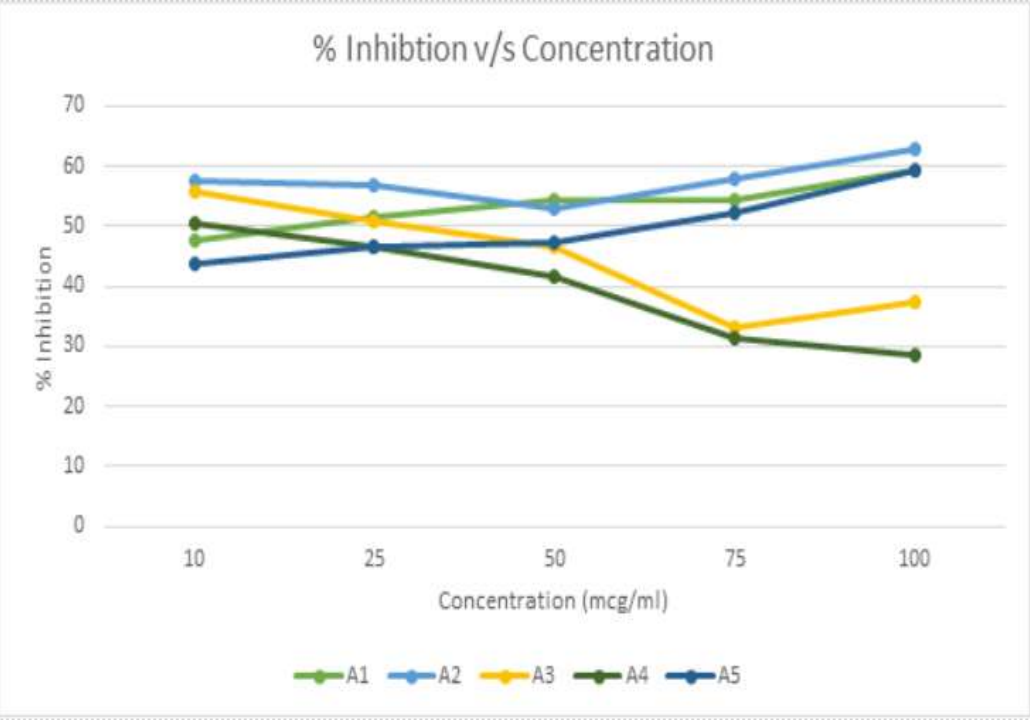


Figure 6: Graph of Percent Inhibition of DPPH v/s Concentration for each of the Derivative

Statistical Analysis

A Friedman's Test was conducted to statistically verify the relevance of concentration dependent change in antioxidant potency of the synthesized derivative, the summary of which has been shown in Table 3. It was observed that $\chi_{statistical} > \chi_{critical}$ and p-value < α. Hence, an inference was made that these derivatives demonstrated significant antioxidant activity.

Parameter	Value
$\chi_{statistical}$	12.52
$\chi_{critical}$	9.49
p- value	0.014
α	0.05

Table 3: Summary of Statistical Parameters

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CONCLUSION

The research presented the synthesis, structural characterisation and evaluation of antioxidant efficacy of five novel Schiff base derivatives of Isatin, aiming to identify potent antioxidant products to combat oxidative stress and in turn a key factor influencing the precipitation of various pathological conditions. Amongst the synthesized derivatives screened for antioxidant activity through DPPH assay, compound A1 and A5, 2,3 dichlorobenzaldehyde and 4-bromo benzaldehyde derivative respectively, emerged as the most potent, showing remarkable concentration dependent free radical scavenging activity, indicative of its strong antioxidant capability. Statistical validation further emphasized the significance of these concentration dependent biological activity.

These encouraging results indicate that specific structural features in the Isatin-Schiff base scaffold contribute to their radical scavenging efficacy and warrant further in-depth investigations for understanding the mechanism of action of these Isatin derivatives. Detailed exploration into their structure-activity relationships (SAR) and pharmacokinetic profiles are necessary to assess their drug-likeness and therapeutic potential. Nonetheless, the promising biological activity of these novel title compounds positions them as valuable lead compounds for future drug development. With further optimization, they could contribute significantly to the development of multifunctional therapeutic agents targeting oxidative stress and other pathological condition.

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