Research Article

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# Synthesis characterization and biological activities of Schiff bases of Isatin

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## ABSTRACT

In the present study, five new Schiff bases of Isatin were synthesized. These new compounds were formed through the condensation reaction between Isatin with 2-aminobenzoicacid, 4-aminobenzoicacid, urea, thiourea and, Pyridin-2-amine. The synthesized compound structures were characterized by FT-IR and $H^1$NMR spectroscopy. The biological activities of the compounds were predicted by using PASS (online software for bioactivity prediction).The newly synthesized Schiff bases of , (3Z)-3-[(pyridin-2-yl)imino]-2,3-dihydro-1H-indol-2-one has shown twitching activity, Nicotinic alpha2beta2 receptor antagonist and fibrillation atrial activity. 2-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid shows better activity in acute neurological disorder. [(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]thiourea acts as a best Thioredoxin inhibitor.4-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid was found to have hypothermic activity.

**Keywords:** Isatin, 2-aminobenzoicacid, 4-aminobenzoicacid, urea, thiourea, Pyridin-2-amine, PASS.

## INTRODUCTION

Isatin (2, 3-dioxindole) has been recently found to exhibit endogamous activity in mammals [1]. In recent years Schiff's and Mannich bases of Isatin were reported to exhibit broadspectrum chemotherapeutic properties such as antibacterial[2-8], antifungal [2-8], anti HIV [3-8], antiviral [9-10],anticonvulsant [11-14], antitubercular [15-17] and anticancer activity [18-20].

Knowing the importance of Schiff bases derived from Isatin from various literature sources, We plan to synthesise, characterize and predict the bioactivity of Schiff bases using online software, PASS (Prediction of Activity Spectra for Substances),which is commonly used technique in drug discovery and development. PASS predict the biological activity spectrum for a compound on the basis of its structural formula. It helps in finding most probable new leadswith required activity spectra among the compounds from in-house andcommercial data bases [21-23].

PASS is a software product designed as a tool for evaluating the general biological potential of an organic drug-like molecule. PASS provides simultaneous predictions of many types of biological activity based on the structure of organic compounds. It can predict more than 1500 pharmacological effects, molecular mechanism of action, and toxicities on basis of structural descriptors of compounds. Thus, PASS can be used to estimate the biological activity profiles for virtual molecules, prior to their chemical synthesis and biological testing.

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**Pa** (probability to be active) estimates the chance that the studied compound is belonging to the sub-class of active compounds resembles the structures of molecules, which are the most typical in a sub-set of actives in PASS training set.

**Pi** (probability to be inactive) estimates the chance that the studied compoundis belonging to the sub-class of inactive compounds resembles thestructures of molecules, which are the most typical in a sub-set of inactives in PASS training set.

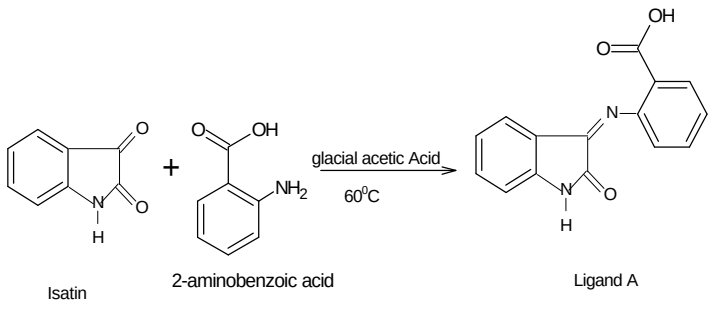
## MATERIALS AND METHODS:

All chemicals used in the present work, viz., Isatin, 2-aminobenzoicacid, 4-aminobenzoic acid, urea, thiourea,pyridin-2-amine and solvents were of analytical reagent (A.R.) grade. The FT-IR spectra of schiff base of isatin were obtained as potassium bromide discs in the range of 400-4000$cm^{-1}$ on a shimadzu spectrophotometer. The 300MHz $^1$H-NMR spectra of the Schiff base of Isatin in DMSO-$d^6$ was recorded on Bruker using tetramethylsiliane as internal standard.

### Preparation of Ligand A:

The synthesis of Schiff base is presented in **Scheme- I.** The ethanolic solution of (25ml) Isatin (0.001M) is mixed with ethanolic solution of (25ml) 2-aminobenzoic acid (0.001M) and adds 3-4 drops of glacial acetic acid. Then the mixture is stirred for 2hours by using magnetic

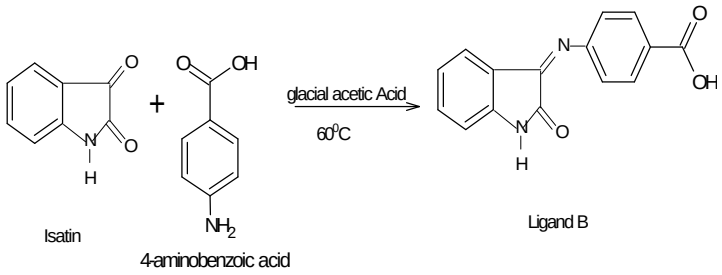
stirrer at 60°C. The product obtained after the evaporation of solvent was filtered, washed with ethanol and recrystallised from ethanol.




**Scheme- I**

**Preparation of Ligand B:**

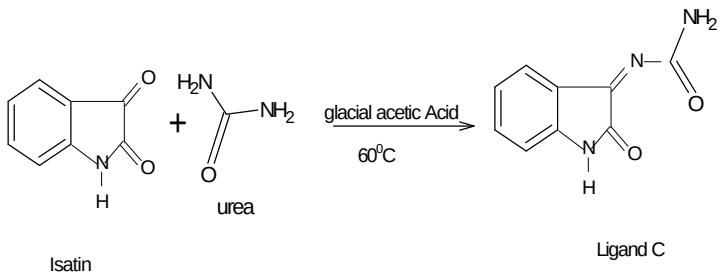
The synthesis of Schiff base is shown in **Scheme- II.** The ethanolic solution of (25ml) Isatin (0.001M) is mixed with ethanolic solution of (25ml) 4-aminobenzoic acid (0.001M) and adds 3-4 drops of glacial acetic acid. Then the mixture is stirred for 2hours by using magnetic stirrer at 60°C. The product obtained after the evaporation of solvent was filtered, washed with ethanol and recrystallised from ethanol.




**Scheme- II**

**Preparation of Ligand C:**

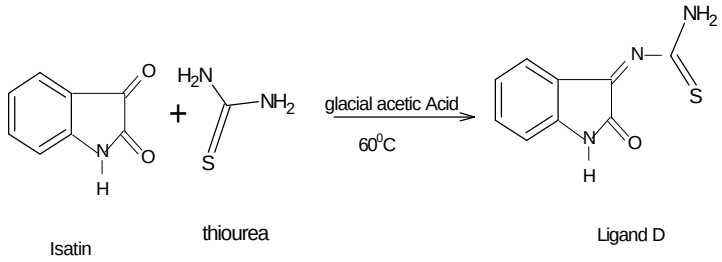
The synthesis of Schiff base is shown in **Scheme- III.** The ethanolic solution of (25ml) Isatin (0.001M) is mixed with ethanolic solution of (25ml) urea (0.001M) and adds 3-4 drops of glacial acetic acid. Then the mixture is stirred for 2hours by using magnetic stirrer at 60°C. The product obtained after the evaporation of solvent was filtered, washed with ethanol and recrystallised from ethanol.




**Scheme- III**

**Preparation of Ligand D:**

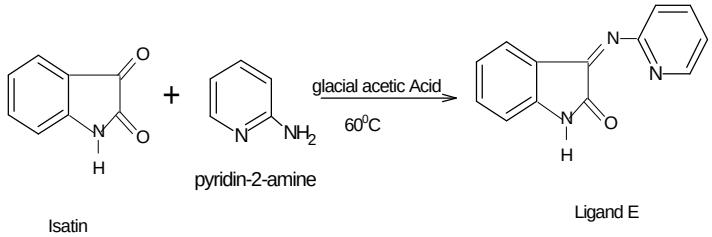
The synthesis of Schiff base is presented in **Scheme- IV.** The ethanolic solution of (25ml) Isatin (0.001M) is mixed with ethanolic solution of (25ml) thiourea (0.001M) and adds 3-4 drops of glacial acetic acid. Then the mixture is stirred for 2hours by using magnetic stirrer at 60°C. The product obtained after the evaporation of solvent was filtered, washed with ethanol and recrystallised from ethanol.




**Scheme- IV**

**Preparation of Ligand E:**

The synthesis of Schiff base is presented in **Scheme- V.** The ethanolic solution of (25ml) Isatin (0.001M) is mixed with ethanolic solution of (25ml) pyridine-2-amine(0.001M) and adds 3-4 drops of glacial acetic acid. Then the mixture is stirred for 2 hours by using magnetic stirrer at 60°C. The product obtained after the evaporation of solvent was filtered, washed with ethanol and recrystallised from ethanol.




**Docking**

The possible bioactivities of all the molecules were predicted with PASS software (V. Poroikov et al, version 1.917). Opening the PASS online software the window appeared as given in **Fig.1.**


**Fig.1 PASS Prediction Window**

The bioactivity result of the synthesized compound appears on the new window as given in **Fig.2.**


**Fig.2. PASS Prediction of (3Z)-3-[(pyridin-2-yl)imino]-2,3-dihydro-1H-indol-2-one.**

## RESULT

**Table-1 Important IR frequencies ($cm^{-1}$) of the Schiff base ligands**

| S.No. | Compd | $u_{C=O}$ | $u_{C=O}$ | $u_{N-H}$ | $u_{-OH}$ | $u_{C=N}$ | $u_{NH2}$ |
|---|---|---|---|---|---|---|---|
| 1. | A | 1728.22 | 1616.35 | 3373.80 | 3473.80 | 1604 | - |
| 2. | B | 1730 | 1624 | 3320 | 3454 | 1615 | - |
| 3. | C | 1715 | 1636 | 3334 | - | 1598 | 3225 |
| 4. | D | 1721 | 1640 | 3351 | - | 1581 | 3270 |
| 5. | E | 1735 | 1625 | 3360 | - | 1612 | - |

**Table-2 Important $^1$H-NMR signals (d, ppm) of the Schiff base ligands**

| S.No. | Compd | $^1$H-NMR(d,ppm) |
|---|---|---|
| 1. | A | Indole nucleus signals at 6.6 (d), 6.5 (t), 6.4 (d). Carboxylicacid signal at 10.1 (s). Aromatic nucleus signals at 5.8 (d), 6.02 (t), 6.18 (t)and 5.69 (d) |
| 2. | B | Indole nucleus signals at 6.9(d), 7.35 (t), 7.18(d), 7.19(t). Carboxylic acid signal at 12.44(s). Aromatic nucleus signals at 7.90(d), 7.28(t), 7.28(t), 7.90(d). |
| 3. | C | Indole nucleus signals at 7.91(d), 7.18(t), 7.35(t), 6.90(d). Amine signal at 7.92(s) |
| 4. | D | Indole nucleus signals at 7.91(d), 7.18(t), 7.35(t), 6.90(d). Amine signal at 7.67(s) |
| 5. | E | Indole nucleus signals at 7.91(d), 7.18(t), 7.35(t), 6.90(d). Heterocyclic ring signals at 6.62(d), 8.40(d), 7.18(t), and 7.70(t). |

**Table-3 PASS prediction activities of Isatin Schiff bases**

| S.No | Name of activity | Name of the compound | Pa | Pi |
|---|---|---|---|---|
| 1. | Twitching | E | 0.858 | 0.014 |
| 2. | Nicotinic alpha2beta2 receptor antagonist | E | 0.830 | 0.007 |
| 3. | Acute neurological disorder | A | 0.797 | 0.009 |
| | | B | 0.642 | 0.028 |
| | | D | 0.647 | 0.027 |
| 4. | Hypothermia | A | 0.710 | 0.013 |
| | | B | 0.749 | 0.009 |
| 5. | Fibrillation, atrial | C | 0.685 | 0.043 |
| | | D | 0.753 | 0.024 |
| | | E | 0.757 | 0.024 |
| 6. | Gastrointestinal hemorrhage | A | 0.737 | 0.001 |
| | | B | 0.485 | 0.021 |
| | | C | 0.482 | 0.010 |
| | | D | 0.480 | 0.010 |
| | | E | 0.690 | 0.026 |
| 7. | Thioredoxin inhibitor | C | 0.644 | 0.018 |
| | | D | 0.704 | 0.009 |
| | | E | 0.697 | 0.011 |
| 8. | Superoxide dismutaseinhibitor | A | 0.721 | 0.001 |
| | | B | 0.442 | 0.091 |
| | | C | 0.418 | 0.055 |
| | | D | 0.446 | 0.044 |
| 9. | Shivering | B | 0.720 | 0.066 |
| | | C | 0.510 | 0.013 |
| | | D | 0.511 | 0.013 |

## DISCUSSION

In order to clarify the manner of the Ligand coordination IR spectra on the 400-4000 $cm^{-1}$ range were recorded. The important IR bands presented and assigned in table-1 show the following characteristics:

Isatin have shown the following stretching frequencies.
$u_{NH}$ = 3190 $cm^{-1}$
$u_{CO}$ = 1740 & 1620$cm^{-1}$
$u_{NH}$ = 1400-1100 $cm^{-1}$ (bending vibration).

Isatin 2-aminobenzoicacid Schiff base (Ligand A) have shown IR spectral frequencies at 3473.80$cm^{-1}$ **($u_{OH}$),** 3373.5$cm^{-1}$ ($u_{NH}$), 1728.22 &1616.35$cm^{-1}$ ($u_{CO}$) and 1604$cm^{-1}$ **($u_{C=N}$).**

Isatin 4-aminobenzoicacid Schiff base (Ligand B) have shown IR spectral frequencies at 343454$cm^{-1}$ **($u_{OH}$),** 3320$cm^{-1}$ ($u_{NH}$), 1730 &1624$cm^{-1}$ ($u_{CO}$) and 1615$cm^{-1}$ **($u_{C=N}$).**

Isatin urea Schiff base (Ligand C) have shown IR spectral frequencies at 3334$cm^{-1}$ ($u_{NH}$), 1715&1636$cm^{-1}$ ($u_{CO}$), 1598$cm^{-1}$ **($u_{C=N}$),** and3225 cm-1**($u_{NH2}$).**

Isatin thiourea Schiff base (Ligand D) have shown IR spectral frequencies at 3351$cm^{-1}$ ($u_{NH}$), 1721&1640$cm^{-1}$ ($u_{CO}$) and 1581$cm^{-1}$ **($u_{C=N}$),**3270 $cm^{-1}$ **($u_{NH2}$).**

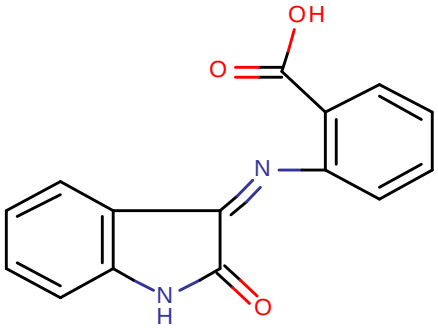
Isatin pyridine-2-amine Schiff base (Ligand E) have shown IR spec-

tral frequencies at 3360cm$^{-1}$ ($u_{NH}$), 1735&1615cm$^{-1}$ ($u_{CO}$) and 1612cm$^{-1}$ **($u_{C=N}$).**

Compare the IR frequencies of Ligand with Isatin. There is a shift in the carbonyl frequency and in the new C=N frequency.

**$^1$H NMR spectral studies**

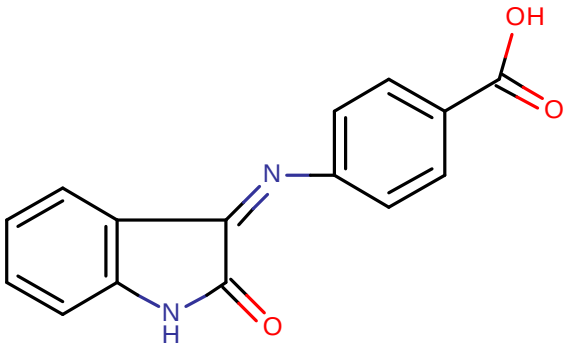
$^1$H NMR spectrum of Isatin2-aminobenzoicacid Schiff base have shown the aromatic indole nucleus signals at 6.6 ppm (doublet), 6.5 ppm (triplet), 6.4 ppm (doublet) and carboxylic acid signal at 10.1 ppm (singlet) and aromatic nucleus signals at 5.8 ppm (doublet), 6.02 ppm (triplet), 6.18 ppm (triplet)and 5.69 ppm (doublet). Hence the **Ligand A** may have the structure




2-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid

**Fig. 3.**

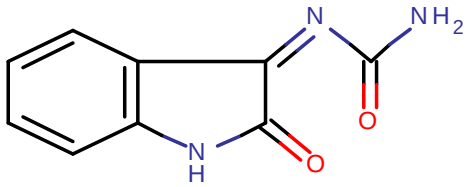
$^1$H NMR spectrum of Isatin4-aminobenzoicacid Schiff base have shown the aromatic indole nucleus signals at 6.6 ppm (doublet), 6.5 ppm (triplet), 6.4 ppm (doublet) and carboxylic acid signal at 10.1 ppm (singlet) and aromatic nucleus signals at 5.8 ppm (doublet), 6.02 ppm (triplet), 6.18 ppm (triplet)and 5.69 ppm (doublet).Hence the **Ligand B** may have the structure




4-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid

**Fig. 4.**

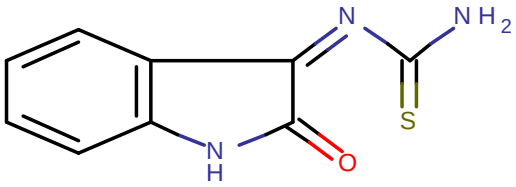
$^1$H NMR spectrum of Isatin urea Schiff base have shown the aromatic Indole nucleus signals at 7.91(d), 7.18(t), 7.35(t), 6.90(d), amine signal at 7.92(s) Hence the **Ligand C** may have the structure




[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]urea

**Fig. 5.**

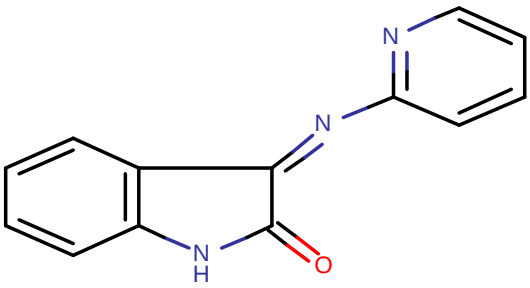
$^1$H NMR spectrum of Isatin thiourea Schiff base have shown the aromatic indole nucleus signals at 7.91(d), 7.18(t), 7.35(t), 6.90(d). Amine signal at 7.67(s). Hence the **Ligand D** may have the structure




[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]thiourea

**Fig.6.**

$^1$H NMR spectrum of Isatin pyridine-2-amine Schiff base have shown the aromatic indole nucleus signals at 7.91(d), 7.18(t), 7.35(t), 6.90(d).Heterocyclic ring signals at 6.62(d), 8.40(d),7.18(t), and 7.70(t). Hence the **Ligand E** may have the structure




(3Z)-3-[(pyridin-2-yl)imino]-2,3-dihydro-1H-indol-2-one

**Fig.7.**

**Twitching**

It is a process of quick movement of a muscle, which cannot be controlled by us. It is a Muscle contraction and relaxation process. The twitching activity of(3Z)-3-[(pyridin-2-yl)imino]-2,3-dihydro-1H-indol-2-one(Pa=0.858) was found to be greater than 80%.

**Nicotinic alpha2beta2 receptor antagonist**

Nicotinic receptors are located post-synaptically in all autonomic ganglia and at the NMJ. At these junctions nicotinic receptors function as the excitatory receptor for the postsynaptic cell. Release of a sufficient quantity of ACh from the adjoining presynaptic cell causes an excitatory response in autonomic ganglion cells and in somatic

muscle fibers. The PASS prediction of nicotinic alpha2beta2 receptor antagonist activity of (3Z)-3-[(pyridin-2-yl)imino]-2,3-dihydro-1H-indol-2-one(Pa=0.830) was found to be greater than 80%.

**Acute neurological disorder**

A neurological disorder is any disorder of the body's nervous system. Structural, biochemicalor electrical abnormalities in the brain, spinal cord or other nerves can result in a range of symptoms. The PASS prediction of acute neurological disorder activity of Schiff bases such as 2-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid(Pa=0.797), 4-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid(Pa=0.642), [(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]thiourea(0.647) were found to be greater than 64%.

**Hypothermia**

Hypothermia is a condition in which core temperature drops below the required temperature for normal metabolism and body functions which is defined as 35.0 °C(95.0 °F).The PASS prediction of 2-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid(Pa=0.710), 4-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid(Pa=0.749),Schiff bases were found to possessed hypothermic activities was greater than 70%.

**Fibrillation, atrial**

Atrial fibrillation is the most common cardiac arrhythmia (irregular heart beat). It may cause no symptoms, but it is often associated with palpitations, fainting, chest pain, orcongestive heart failure. The fibrillation atrial activity was observed in Schiff bases such as [(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]urea (Pa=0.685),[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]thiourea(Pa=0.753), (3Z)-3-[(pyridin-2-yl)imino]-2,3-dihydro-1H-indol-2-one(Pa=0.757).The atrial fibrillation activity was found to be greater than 65%.

**Gastrointestinal hemorrhage**

Gastrointestinal hemorrhage is bleeding within the gastrointestinal (GI) tract. The most common underlying conditions are peptic ulcer, Mallory-Weiss syndrome, esophageal varices, diverticulosis, ulcerative colitis, and carcinoma of the stomach and colon. 2-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid(Pa=0.737), 4-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid(Pa=0.485),[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]urea(Pa=0.482),[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]thiourea(Pa=0.480), (3Z)-3-[(pyridin-2-yl)imino]-2,3-dihydro-1H-indol-2-one(Pa=0.690).Schiff bases were observed to show gastrointestinal hemorrhage activities were ranges from 48% to 73%.

**Thioredoxin inhibitor**

Thioredoxin is a class of small redox proteins known to be present in all organisms. It plays a role in many important biological processes, including redox signaling. In humans, it is encoded by the *TXN* gene. It act as antioxidants by facilitating the reduction of other proteins by cysteine thiol-disulfide exchange.[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-lidene]urea(Pa=0.644), [(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]thiourea(Pa=0.704), (3Z)-3-[(pyridin-2-yl)imino]-2,3-dihydro-1H-indol-2-one(Pa=0.697).Schiff bases were observed to show Thioredoxin inhibitor activities was greater than 64%.

**Superoxide dismutaseinhibitor**

These are enzymes that catalyze the dismutation of superoxide into oxygen and hydrogen peroxide. Thus, they are an important antioxidant defense in nearly all cells exposed to oxygen.SOD has powerful antinflammatory activity. 2-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid(Pa=0.721), 4-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid(Pa=0.442), [(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]urea(Pa=0.418), [(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]thiourea(Pa=0.446).Schiff bases were found to show superoxide dismutase inhibitor activities were ranges from 40% to 72%.

**Shivering**

Shivering is a bodily function in response to early hypothermia in warm-blooded animals. Shivering can also be a response to a fever, as a person may feel cold, though their core temperature is already elevated.4-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino} benzoic acid(Pa=0.720), [(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]urea(Pa=0.510), [(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]thiourea(Pa=0.511).Schiff bases were found to show superoxide dismutase inhibitor activities were ranges from 50% to 72%.

**CONCLUSION**

A new Schiff bases were synthesized by treating Isatin with 2-aminobenzoicacid, 4-aminobenzoicacid, urea, thiourea and, Pyridin-2-amine. The spectroscopy analysis of FT-IR, and $^{1}$H-NMR were in good agreement with the proposed structure **(fig.3-7)**. The five newly synthesized Schiff bases of our work, (3Z)-3-[(pyridin-2-yl)imino]-2,3-dihydro-1H-indol-2-one has more biological activities such as twitching, Nicotinic alpha2beta2 receptor antagonist, Fibrillation atrial, Thioredoxin inhibitor and, Gastrointestinal hemorrhage of 85.8%, 83.0%, 75.7%,69.7% and, 69.0% respectively. 2-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid has biological activities such as Acute neurological disorder, Gastrointestinal hemorrhage, Superoxide dismutase inhibitor and, hypothermia of 79.7%, 73.7%, 72.1% and, 71.0% respectively.[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]thiourea has predominant activities as Fibrillation atrial and, Thioredoxin inhibitor of 75.3% and 70.4% respectively.4-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid shows activities such as hypothermic activity and shivering of 74.9% and 72% respectively. [(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]urea has shown fibrillation atrial activity of 68.5%. Therefore we conclude that among the newly synthesized Schiff bases, (3Z)-3-[(pyridin-2-yl)imino]-2,3-dihydro-1H-indol-2-one has shown better twitching activity , Nicotinic alpha2beta2 receptor antagonist and fibrillation atrial activity.2-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid shows better activity in acute neurological disorder. [(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]thiourea acts as a best Thioredoxin inhibitor.4-{[(3Z)-2-oxo-2,3-dihydro-1H-indol-3-ylidene]amino}benzoic acid has shown better hypothermic activity.

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