*Available online at* www.joac.info

ISSN: 2278-1862

**Journal of Applicable Chemistry**

**2014, 3 (1): 426-432**

(International Peer Reviewed Journal)

# Synthesis And Characterization Of Some Biologically Important Isatin Derivatives

**Ratnesh Das* and Arti Saxena**

*Department of Chemistry, Dr.HariSingh Gour University, A Central University, Sagar (M.P.) 470003 **INDIA**

Email: ratnesh_das1@yahoo.co.in

Accepted on 16th January 2014

## ABSTRACT

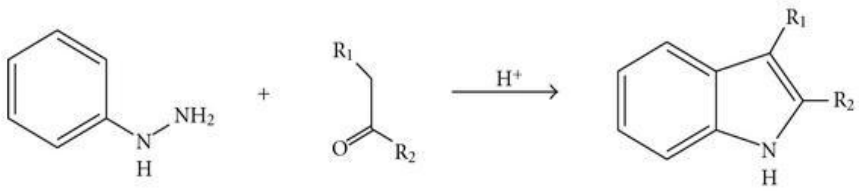
*Isatins (1H-indole-2,3-dione) are synthetically versatile substrates, where they can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines, and as raw material for drug synthesis. Isatin have also been found in mammalian tissue and their function as a modulator of biochemical processes has been the subject of several discussions. This review represents some synthesized Isatin derivatives and their pharmacological profiles which may contribute in future to synthesize various analogs and to develop new pharmacologically less toxic medicines. In this study a new series of Isatin 3 hydrazone derivatives was synthesized. Structure of the title compound was characterized by spectral techniques like FT-IR and $^{1}H$ NMR.*

**Keywords:** Isatin 3 hydrazones and its derivatives.

## INTRODUCTION

Isatin (2,3-dioxindole) is an endogenous compound identified in humans, and its effect has been studied in a variety of systems. Isatin nucleus having both the keto and lactam moiety has aroused tremendous curiosity due to its diverse biological and pharmacological studies.

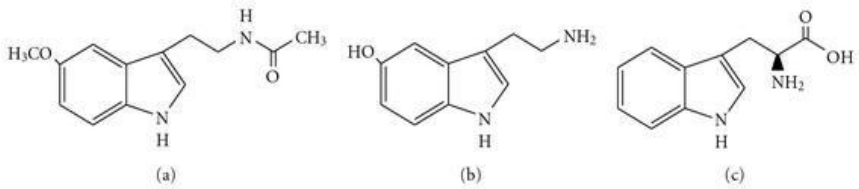
Isatin or 1H-indole-2,3-dione is an indole derivative. The compound was first obtained by Erdman1 and Laurent2 in 1841 as a product from the oxidation of indigo dye by nitric acid and chromic acids. The compound is found in many plants. In recent years, indole derivatives have acquired conspicuous significance due to their wide spectrum of biological activities. From literature survey it is well known that isatin heterocycles exhibit manifold importance in the field of medicinal chemistry as a potent chemotherapeutic agent. Biological properties of isatin include a range of actions in the brain and offer protection against certain types of infections. Indole is an aromatic heterocyclic compound that has a bicyclic structure. It is an accepted constituent of fragrances and the precursor to many pharmaceuticals. One of the oldest and most reliable methods for synthesizing substituted indoles is the Fischer indole synthesis[1].



**Scheme 1**. Fischer indole synthesis

Indoles are present in many important biological compounds. Tryptophan is a significant indole derivative while serotonin and melatonin are biochemically active indole molecules. There are also many indole alkaloid derivatives found in nature. The plant hormone Auxin contains indol-3-acetic acid. Furthermore, there are many important indole derivatives used in treatment. The anti-inflammatory drug indomethacin, the betablocker pindolol, and the naturally occurring hallucinogen dimethyltryptamine are some of the important indole derivatives. Indole derivatives represent many important classes of therapeutical agents in medicinal chemistry such as anticancer[2], antioxidant[3] ,and anti-HIV[4-5].Furthermore, some indole derivatives, such as melatonin and serotonin, influence many important biochemical processes. They act as antioxidant and play an important role in the immune system[6-9].

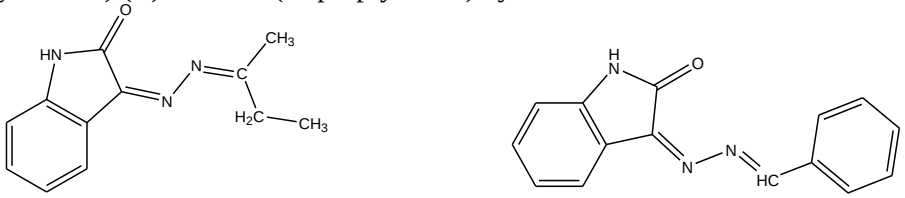
Melatonin, is an indole ring containing hormone produced in the brain by the pineal gland, from the amino acid tryptophan. It has a significant role in the protection of nuclear and mitochondrial DNA.



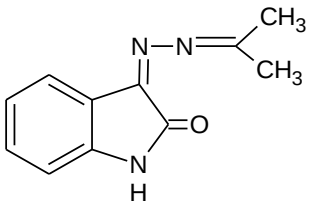
a. Melatonin b. Serotonin c. tryptophan

Synthetically versatile heterocycle, isatin (indole 2,3-dione) is well known to act as a potent endo- genous neurochemical regulator in brain in mammals.1,2 Isatin's concentration in urine is to become a diagnostic marker for the clinical severity of Parkin- son's disease in humans however electrophysiology, synthetic and metabolic pathways of isatin in human system are yet to be fully established.

In recent years Indole and its derivatives like isatin are known to be associated with broad spectrum of biological activity like antibacterial[10], anti-inflammatory[11], analgesic[12], anti- viral[13], antifungal[14], anti-tubercular[15], anti-depressant. Isatin hydrazones have been reported to possess anticonvulsant, activity also. In view of these facts and as a continuation of our work in the laboratory, prompted us to synthesize some new (A) isatin-3-(methyl ethylidene) hyrdazone (B) isatin-3-(benzylidene)hydrazone),(C) isatin -3-(isoproplylidene) hydrazone.



(A) (B)



(C)

All the synthesized compounds were screened for their in vitro anti-bacterial and anti-fungal activity. isatin are well known electroactive compounds that are readily oxidized at carbon-based electrodes, for example, glassy carbon electrode. Voltammetric techniques in general, and differential pulse voltammetry (DPV) in particular, are considered to be useful tools for the determination of indole derivatives.

## MATERIALS AND METHODS

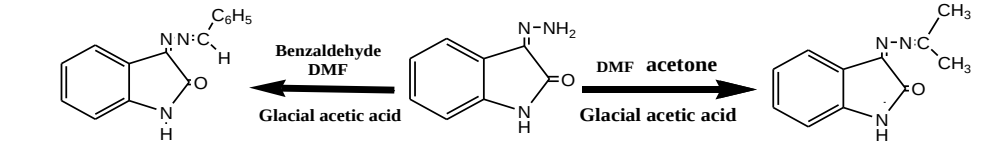
**Drugs and Chemicals:** A typical synthetic strategy employed to obtain the title compound in excellent yield is depicted in scheme 1 .In the present investigation, isatin 3 hydrazone were obtained from reaction of isatin and hydrazine hydrate in alcoholic medium and subjected to substitution with different aldehyde and ketone. Aldehydr which is used in the substitution : benzaldehyde and ketone :acetone, butanone. All reagents were of the highest purity commercially available.

**Experimental :** The reagents were all analytically pure. All solvents and liquid reagents were dried by standard methods in advance and distilled before use. Isatin and different aldehyde and ketone were bought from the Sigma aldrich ltd.Reaction are monitored by thin-layer chromatrography (TLC) on sillicagel 60 $F^{254}$ aluminium sheet .The mobile phase was benzene: chlorfom: methanol (27: 9: 4) and detection was made using iodine chamber. The infrared (IR) spectra were recorded on a FTIR-8310 Shimadzu spectrometer using potassium bromide pellets. 1H NMR spectra were recorded on a JEOL AL3OO FTNMR , Chemistry Department, Banaras Hindu University, Varanasi-221005 in CDCl3 or DMSO-d6 with TMS as the internal reference The chemical shifts are expressed in ppm downfield from the internal standard; the coupling constants are in Hz, and signals are quoted as*s*(singlet), *d*(doublet), *t* (triplet), *q* (quartet), or *m* (multiplet). Melting points were determined using open capillary tube in Toshniwal Melting point apparatus and are presented without any correction.

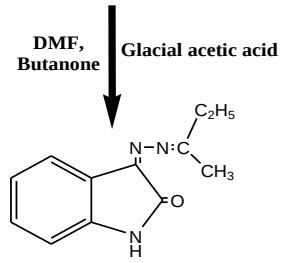
**Synthesis and Reaction Scheme:** Oxygenated indole derivatives indole 2,3 dione also name as isatin has been found anti microbial agent in the field of pharmacology. Indole 2,3 dione react with hydrazine hydrate in the presence of ethylalchol formed isatin 3- hydrazone. This is basic compound for forming indole derivatives.

**Synthesis of Isatin 3- Hydrazone:** An appropriate isatin (indole-2,3-dione) ( 0.01 mol) was dissolved in ethylalcohol alcohol (20 ml) and added hydrazine hydrate (0.015 mol) while shaking. The reaction mixture was stirred well, warmed on a water-bath for 10 min and left in the refrigerator for 3 h. The resultant yellow crystalline solid was filtered, washed repeatedly with small portions of cold water and finally with a small quantity of cold alcohol. The product was dried and purified by recrystallization from ethylalcohol. M.P. 220°C, Yield; 74.5%

**Synthesis of Isatin 3- Hydrazone Derivatives:** Isatin -3-hydrazone (0.1 mol) and appropriate aldehyde or ketone(0.1mol),DMF (30ml) and glacial acetic acid(10ml) were keptbat 60°C on water bath for half an hr with vigorous stirring. The reaction mixture was poured into water (300ml) and recrystallized from ethanol solvent.

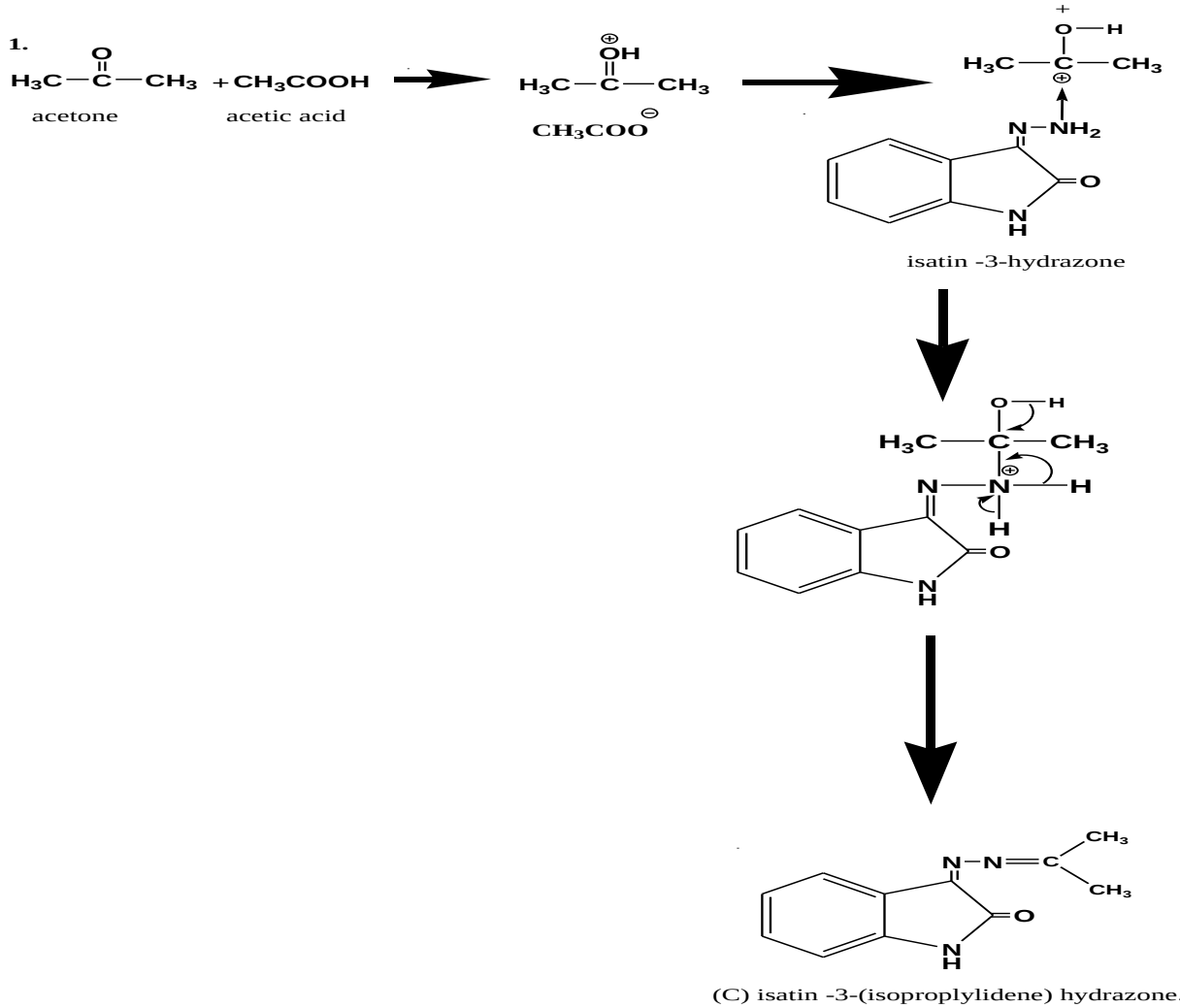



**isatin-3-(acetobenzylidene)hydrazone** **isatin-3-hydrazone** **isatin -3-(isoproplylidene) hydrazone.**



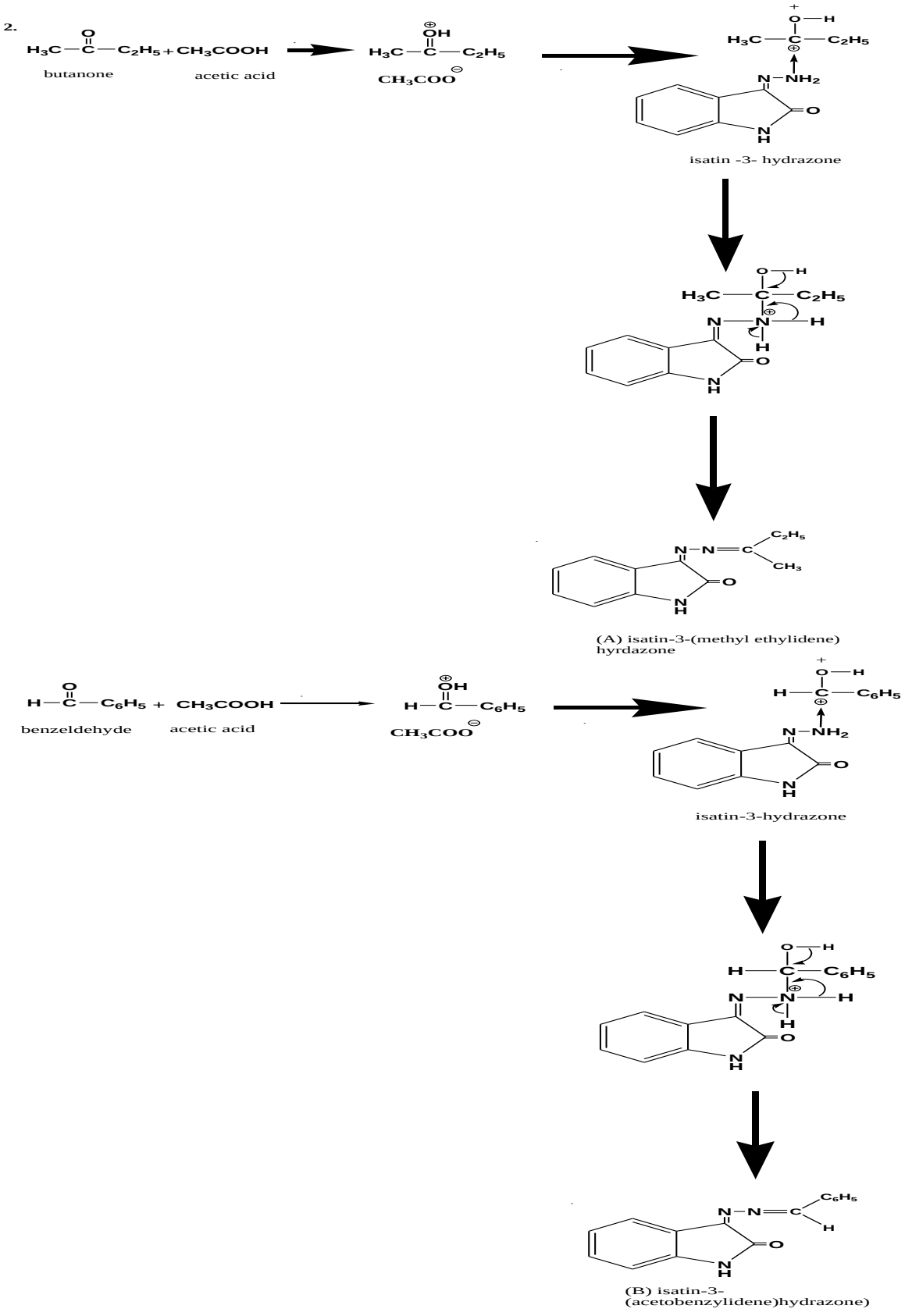

**Isatin-3-(methyl ethylide)hydrazone**

Reaction Mechanism:




isatin -3-hydrazone

(C) isatin -3-(isoproplylidene) hydrazone.


2.
butanone
acetic acid
isatin -3- hydrazone
(A) isatin-3-(methyl ethylidene) hyrdazone
3.
benzeldehyde
acetic acid
isatin-3-hydrazone
(B) isatin-3-(acetobenzylidene)hydrazone)

**Characterization:**

**Infrared Spectrum ($cm^{-1}$ , KBr) :** Isatin 3- hydrazone were obtain by reaction of isatin with hydrazone hydrate and its derivatives (A,B,C) obtained by the reaction of various aldehyde and ketone with it. The IR spectra of parent compound were taken between 4000 $cm^{-1}$-600 $cm^{-1}$ spectrum of compound absorb at 3350 $cm^{-1}$, show the presence of –CONH Group and 3148 $cm^{-1}$ band is due to NH-NH Group. The absorption band at 2932 $cm^{-1}$ indicates the presence of aromaticity and disubstitution at benzene ring. The absorption band at 1656 $cm^{-1}$ show the presence of =CO and C-N Groups. Whereas band at 1590 $cm^{-1}$ due to -N-N Group. H-N-H Bending scissoring (in plane) absorption at 1550 $cm^{-1}$-1680 $cm^{-1}$ and wagging (out of plane) at 650 $cm^{-1}$ to 950 $cm^{-1}$.

1H NMR Data - (ppm, 300MHz,TMS) : 6.70-7.91 ( m, Ar-H ), 11.19(s,1H indole NH), 8.5 ( s , $NH_2$) Compound (A) absorption at 3368 $cm^{-1}$ due to –NH and –CONH, Absorption at 3152 $cm^{-1}$ due to aroaticity and disubstitution on benzene ring, absorption at 1652 $cm^{-1}$ due to =CO,=C=N,C-C, absorption at 1586 $cm^{-1}$ due to -N-N Groups, absorption at 1464 $cm^{-1}$ due to –C-CH3.

1H NMR DATA- (ppm, 300MHz,TMS) : 6.70-7.91 ( m, Ar-H ), 11.19(s,1H indole NH) 11.19 (s , $CH_3$ proton).Compound (B) absorption at 3500 c.m.-1 due to CONH Group and absorption at 1345 $cm^{-1}$ due to =CO- Group, 1650 $cm^{-1}$ due to - C-N , 1470 $cm^{-1}$ due to N-N ,3320 $cm^{-1}$ due to N-H and –CONH Groups

1H NMR DATA- (δ ppm, 300MHz,TMS) : 6.70-7.91 ( m, Ar-H ), 11.19(s,1H indole NH), 3.28 (s,phenyl ring proton) 2.5 (s , CH-) . Compound (C) absorption at 1465 $cm^{-1}$ due to C-CH3 Group and absorption at 1665 $cm^{-1}$ due to N=C Group . Absorption at 1100 $cm^{-1}$ due to C-C-C Groups. Absorption at 3418 $cm^{-1}$ , 3376 $cm^{-1}$ due to N-H and –CONH Groups .absorption at 1650 $cm^{-1}$ and 1720$cm^{-1}$ due to =CO,CN, C-C Groups.

1H NMR DATA - (ppm, 300MHz,TMS) : 6.9-7.5 (s,-CH3 proton) , 10.5 (s, $CH_3$ in $C_2H_5$ ), 6.70-7.91 ( m, Ar-H ), 11.19(s,1H indole NH)

## RESULTS AND DISCUSSION

Azine are prepared by reaction of isatin 3 hydrazone with different aldehyde and ketone. Isatin 3 hydrazone is basic unit of azine series. As many as new indole derivatives compounds were synthesized by reaction of isatin 3 hydrazone with different aldehyde (benzaldehyde) and ketone(acetone, butanone) similar above procedure and then characterized by spectral data. The IR spectra of parent compound were taken between 4000 $cm^{-1}$-600 $cm^{-1}$ spectrum of compound absorb at 3350 $cm^{-1}$, show the presence of –CONH Group and 3148 $cm^{-1}$ band is due to NH-NH Group supporting the formation of Isatin 3 hydrazone . absorption at 1464 $cm^{-1}$ due to –C-CH3 supporting the formation of compound C. absorption at 1504 $cm^{-1}$ due to –C-$C_2H_5$ supporting the formation of compound A. In 1HNMR spectra signal at 2.5 (s, CH-) supporting the formation of compound B. The details of some of the representative compounds formula, molecular weight, melting point % yield of each compound is given in the table 1. All the synthesized compounds were tested for *in vitro* antimicrobial activity. The tested compounds exhibit antimicrobial activity against three microbe.

**Table 1**. Yield and Melting Points of Synthesised Compounds.

| Sr. No | COMPOUND | SUBSTITUENT | MOLECULAR FORMULA | MELTING POINT | MOLECULAR WEIGHT | YEILD % |
|---|---|---|---|---|---|---|
| 1 | A | $CH_3COC_2H_5$ | $C_{10}H_{13}N_2O$ | 207-209 | 177 | 90.52 |
| 2 | B | $C_6H_5CHO$ | $C_{15}H_{11}N_2O$ | 178 | 235 | 89.30 |
| 3 | C | $CH_3COCH_3$ | $C_{11}H_{11}N_2O$ | 199-200 | 187 | 90.30 |

## APPLICATIONS

These results may contribute in future to synthesize various analogs of Isatin and to develop new pharmacologically less toxic medicines.

## CONCLUSIONS

This report easy, a simple and convenient route for the synthesis of novel biologically active isatin derivatives.

## ACKNOWLEDGEMENT

I Express my thanks to Dr. Harisingh Gour University, Sagar (M.P.) for characterization of sample. The UGC, New Delhi, for the financial support in the form of research fellowship.

## REFERENCES

[1] E. Fischer and F. Jourdan, "Ueber die Hydrazine der Brenztraubensäure," Berichte der deutschen chemischen Gesellschaft, **1883**, 16, 2241–2245.
[2] I. Chen, S. Safe, and L. Bjeldanes, *Biochemical Pharmacology*, **1996**, 51, 1069–1076.
[3] S. Suzen and E. Buyukbingol, *Il Farmaco*, **2000**, 55, 246–248.
[4] E. Buyukbingol, S. Suzen, and G. Klopman, **1994**, 49, 443–447.
[5] S. Suzen and E. Buyukbingol, *Il Farmaco*, **1998**, 53, 525–527.
[6] M. Valko, H. Morris, and M. T. D. Cronin, *Current Medicinal Chemistry*, **2005**, 12, 1161–1208.
[7] A. M. S. Poon, Z. M. Liu, C. S. Pang, G. M. Brown, and S. F. Pang, *Biological Signals*, **1994**.
[8] P. M. Liebmann, A. Wölfler, P. Felsner, D. Hofer, and K. Schauenstein, *International Archives of Allergy and Immunology*, **1994** , 112, 203–211.
[9] F. Lezoualc'h, T. Skutella, M. Widmann, and C. Behl, *NeuroReport*, **1996**, 7, 2071–2077.
[10] V.Alagarsamy, S.Meena, R.Revathi, *Indian J.Pharm. Sci.*, **2004**, 4: 459- 62.
[11] V.Alagarsamy, K.V.Ramseshu, *Pharmazie*, **2003**, 58,233-36.
[12] S.K.Sridhar, M.Sreenivasulu, *Indian drugs*, **2001**, 38,531-34.
[13] S.N.Pandeya, D.Sriram, G.Nath ,E.DeClercq , *Eur. J. Pharm. Sci.* **1999**, 9,25-31.
[14] R.S.Verma, W.Nobles, *J. Pharm. Sci.***, 1975**, 69: 881-882.
[15] V.H.Tran, Q.D.Nguyen, N.V.Le, *Tap. Chi. Dou Hoc.* **2002**, 8, 15-17.