

**Facile Synthesis, and Antimicrobial activity of Imidazole derivatives by Zirconia NPs catalyst**

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**Abstract**

Imidazole derivatives are considered potential chemical compounds that could be therapeutically effective against several harmful pathogenic microbes. In the present study substituted imidazoles via nano zirconia catalyzed multicomponent reaction of isatin derivatives with ammonium acetate and substituted indole-3- aldehydes has been developed. The synthesized imidazole derivatives were characterised using spectral and analytical data viz; nuclear magnetic resonance (NMR) , IR and <sup>13</sup> CNMR. The results of antibacterial and antifungal and antioxidant activities showed that some of the synthesized compounds exhibited promising activities.

**Key words :** nano ZrO<sub>2</sub>catalyst, Indole-3-aldehyde, imidazole, Isatin,antimicrobial activity.

**Introduction**

Heterocycles form the most complicated and fascinating disciplines of chemistry for more than a century. There is an ample collection of various structures of heterocycles and their economic use as drugs. Among the many heterocycles, nitrogen-comprising heterocyclic molecules have piqued the curiosity of researches during periods of organic synthesis advancement [1]. Among the various chemical compounds explored in medicinal chemistry, imidazole derivatives have attracted significant attention due to their versatile pharmacological properties [2].

Imidazole a five membered heterocyclic compound featuring two non adjacent nitrogen atoms act as a versatile building block in chemistry and biology. This 1,3 diazole is a privileged scaffold for designing drugs with broad spectrum activities. It is the basic core of some important biological building blocks such as histidine and the related hormones histamine. The 1,3-diazole and its containing compounds shows a lot of therapeutic activities such as analgesics, antifungal, antihypertensive, antiobesity, antitumor [3],

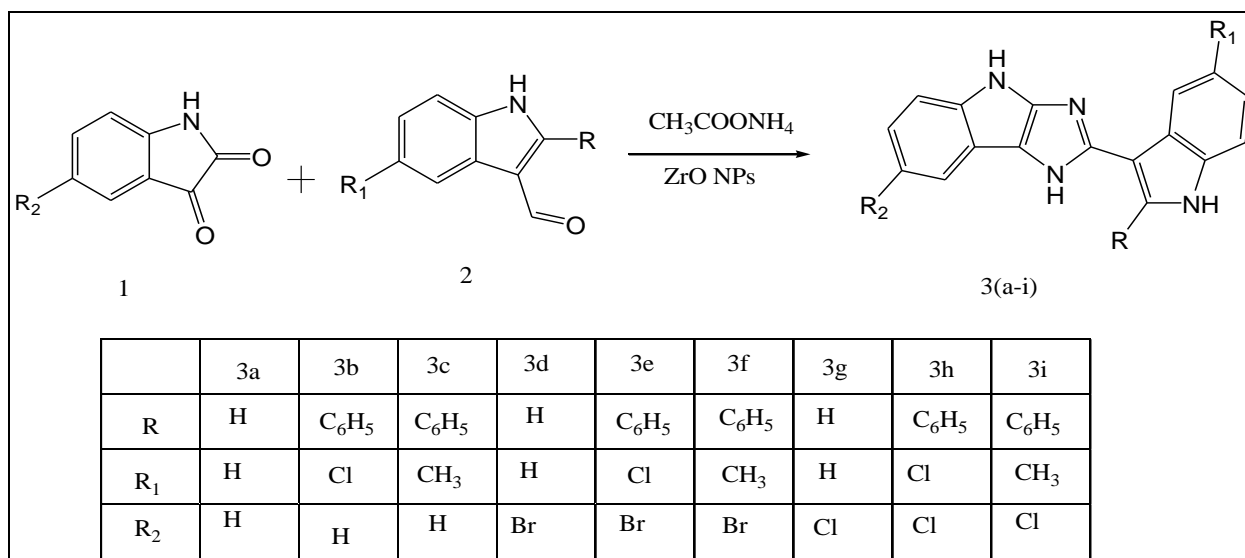
antiviral, anthelmintic, antitubercular [4], antiulcer, antihistaminic [5], anti-inflammatory, antidepressant [6], antidiabetic [7], anticonvulsant [8], antiallergic [9], antirheumatic [10], antiasthmatic, alpha-blockers [11], antiprotozoal [12], antiaging, anticoagulant, antimalarial [13], and antiamoebic activity [14] etc. Imidazoles and their derivatives are associated with a variety of pharmacological activities. Some of the commercially important imidazoles are 1-(1-(2-hydroxy-3-methoxypropyl)-1H-imidazol-2-yl)ethanone (Misonidazole), N-(2,6-dichlorophenyl)-4,5-dihydro-1H-imidazol-2-amine (Clonidine), 2-(6-chloro-2-(4-chlorophenyl)imidazo[1,2-a]pyridin-3-yl)-N,N-dipropylacetamide (Alpidem), 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol (Metronidazole), ethyl 8-fluoro-5-methyl-6-oxo-5,6-dihydro-4H-benzo[f]imidazo[1,5-a][1,4]diazepine-3-carboxylate (Fulmazenil), 2-(4-(2,4-dichlorophenyl)-1,1-dithiolan-2-ylidene)-2-(1H-imidazol-3-yl)acetonitrile (Luliconazole).

Due to their impressive significance, various synthetic routes have been designed for the synthesis of imidazole and its derivatives [15]. In recent times, metal nanoparticles are used as heterogeneous catalysts in organic synthesis mainly because they achieve the objectives of green and sustainable chemistry. Recently scientists have done a lot of work to synthesize precise metal nanoparticles (NPs). The easiness of separation, recovery, and reuse of these NPs further enhance their attractiveness as green and sustainable catalysts [16-18]. Recently, nano zirconia ( $\text{ZrO}_2$ ) has attracted considerable attention due to their wide applicability as a heterogeneous catalyst [19-24].  $\text{ZrO}_2$  nanoparticle catalyst is a cheap, moisture stable, safe, reusable, and commercially available white powder is of big curiosity to many researchers. It has been revealed from the literature that numerous parallel applications of nano zirconia, as an effective catalyst in green/sustainable synthetic chemistry, have already been reported [25-30]. but we choose the greener method of synthesizing imidazole using Zirconia nano particles as catalyst.

The reaction conditions and several parameters for facile synthesis of substituted imidazole was studied by *Sundaram Singh and Shivam Bajpai*. In view of the above, it was thought worthwhile to synthesize some novel imidazoles fused with indole-3-carboxaldehyde nucleus and isatin derivatives because of their high biological profile to yield novel compounds of lethal interest since the combination of two or more different heterocyclic compounds in a single molecule enhances the biological profile incredibly.

## Materials and methods

All the chemicals and solvents were of laboratory reagent grade and used as received from Sigma Aldrich and SD fine. Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by TLC using silica gel-G coated aluminum plates (Merck) and spots were visualized by exposing the dry plates to iodine vapors. The IR(KBr) spectra were recorded on a Perkin-Elmer spectrometer on FT-IR spectrometer. The  $^1\text{H}$  NMR (DMSO- $d_6$ ) spectra recorded on a Bruker (400 MHz) and the chemical shifts were expressed in ppm ( $\delta$  scale) downfield from TMS. Mass spectral data were recorded by electron impact method on JEOL GCMATE II GC-MS mass spectrometer. Elemental analysis was carried out using Flash EA 1112 series elemental analyzer. All the compounds gave C, H and N analysis within  $\pm 0.5\%$  of the theoretical values.



Scheme-1

## Experimental Procedure

### Procedure for the synthesis of ZrO<sub>2</sub>NPs

0.075 M solution of ZrOCl<sub>2</sub>·8H<sub>2</sub>O was prepared and then precipitated with NH<sub>4</sub>OH (25%) with continuous stirring on a magnetic stirrer till the pH raises in the range of 10–10.5. This resulted in the formation of precipitate of zirconium hydroxide. The precipitate was filtered and washed with double distilled water until traces of chloride ion were completely removed from the filtrate. Complete removal of chloride ion from filtrate was checked by titrating it with AgNO<sub>3</sub> solution using potassium chromate as indicator. Now, the

precipitate was dried in oven at 80–90°C for 24 h and calcinated at 600°C for 3 h in order to formation of white nano zirconia powder<sup>31</sup>.

### **procedure for the synthesis of substituted imidazoles 3(a-i).**

To a mixture of isatin derivatives **1** (1 mmol), ammonium acetate (5 mmol), substituted indole aldehydes (**2**) (1 mmol), 15 mol% of ZrO<sub>2</sub>NPs was added (**Scheme 1**). The mixture was heated and stirred at 110°C for 30 min. The progress of the reaction was monitored by thin layered chromatography (n-hexane:ethyl acetate, 1:1). After completion, 20 ml acetone was added to the reaction mixture; the catalyst was removed by filtration and washed with xylene and acetone. Then, 50 ml of double distilled water is added to the liquid portion. This resulted in the formation of precipitate of products (**3a-i**). The precipitate was filtered, dried and recrystallized with ethanol.

## **Experimental**

### **Compound 3a**

IR (KBr) ( $\lambda_{\text{max}}$  in cm<sup>-1</sup>): 3427, 3297(indoleN-H); 3213(imidazole NH) 1278(C=N); 2968 (Ar CH stretch). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ (ppm): 11.70(s, 1H, indoleNH); 11.20(s, 1H, indoleNH); 10.70(s, 1H, imidazoleNH); 7.20-8.10(m, 9H, Ar-H).

LCMS: m/z=193; Analysis: Calcd for: C<sub>17</sub>H<sub>12</sub>N<sub>4</sub>, C(74.98);

H, (4.44); N, (20.58); Found: C, 75.12; H, 4.40; N, 20.67. Brown crystals.

### **Compound 3b**

IR (KBr) ( $\lambda_{\text{max}}$  in cm<sup>-1</sup>): 3431, 3251(indoleN-H); 3224(imidazole NH) 1278(C=N); 2968 (Ar CH stretch). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ (ppm): 11.81(s, 1H, indoleNH); 11.31(s, 1H, indoleNH); 10.60(s, 1H, imidazoleNH); 7.10-8.30(m, 12H, Ar-H).

LCMS: m/z=382; Analysis: Calcd for: C<sub>23</sub>H<sub>15</sub>ClN<sub>4</sub>, C(72.16);

H, (3.95); N, (14.63); Found: C, 72.08; H, 3.91; N, 14.73. Dark yellow crystals..

### **Compound 3c**

IR (KBr) ( $\lambda_{\text{max}}$  in cm<sup>-1</sup>): 3481, 3268(indoleN-H); 3254(imidazole NH) 1278(C=N); 2968 (Ar CH stretch). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ (ppm): 11.60(s, 1H, indoleNH); 11.10(s, 1H, indoleNH); 10.60(s, 1H, imidazoleNH); 7.15-8.2(m, 12H, Ar-H).

LCMS: m/z=362; Analysis: Calcd for: C<sub>24</sub>H<sub>18</sub>N<sub>4</sub>, C(79.54);

H, (5.01); N, (15.46); Found: C, 79.35; H, 5.08; N, 15.41. Light yellow crystals..

### Compound 3d

IR (KBr) ( $\lambda_{\text{max}}$  in  $\text{cm}^{-1}$ ): 3462, 3258(indoleN-H); 3241(imidazole NH)1278(C=N); 2968 (Ar CH stretch).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm):12.20(s,1H,indoleNH);11.30(s,1H,indoleNH);11.10(s,1H,imidazoleNH);7.16-8.40(m,8H,Ar-H).

LCMS:m/z=351;Analysis:Calcd for: $\text{C}_{17}\text{H}_{11}\text{BrN}_4$ ,C(58.14);

H,(3.16);N,(15.95); Found:C,58.08; H,3.11; N,15.89. Dark brown crystals..

### Compound 3e

IR (KBr) ( $\lambda_{\text{max}}$  in  $\text{cm}^{-1}$ ): 3438, 3249(indoleN-H); 3232(imidazole NH)1278(C=N); 2968 (Ar CH stretch).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm):12.30(s,1H,indoleNH);12(s,1H,indoleNH);11.40(s,1H,imidazoleNH);7.35-8.20(m,11H,Ar-H).

LCMS:m/z=461;Analysis:Calcd for: $\text{C}_{23}\text{H}_{14}\text{BrClN}_4$ ,C(59.83);

H,(3..6);N,(12.13); Found:C,59.70; H,3.13; N,12.07. Light yellow crystals..

### Compound 3f

IR (KBr) ( $\lambda_{\text{max}}$  in  $\text{cm}^{-1}$ ): 3435, 3259(indoleN-H); 3232(imidazole NH)1278(C=N); 2968 (Ar CH stretch).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm):12.30(s,1H,indoleNH);12(s,1H,indoleNH);11.40(s,1H,imidazoleNH);7.35-8.20(m,11H,Ar-H).

LCMS:m/z=461;Analysis:Calcd for: $\text{C}_{24}\text{H}_{17}\text{BrN}_4$ ,C(65.32); H,(3..88);N,(12.70);

Found:C,65.40; H,3.81; N,12.62. Light yellow crystals..

### Compound 3g

IR (KBr) ( $\lambda_{\text{max}}$  in  $\text{cm}^{-1}$ ): 3457, 3254 (indoleN-H); 3239(imidazole NH)1278(C=N); 2968 (Ar CH stretch).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 12.30 (s,1H,indoleNH); 11.40,(s,1H,indoleNH);11.10(s,1H,imidazoleNH);7.20-8.40(m,11H,Ar-H).

LCMS:m/z=306; Analysis: Calcd for:  $\text{C}_{17}\text{H}_{11}\text{ClN}_4$ ,C(66.56); H,(3.61);N,(18.26);

Found:C,66.41; H,3.67; N,18.20 Light yellow crystals..

### Compound 3h

IR (KBr) ( $\lambda_{\text{max}}$  in  $\text{cm}^{-1}$ ): 3438, 3262 (indoleN-H); 3223(imidazole NH)1278(C=N); 2968 (Ar CH stretch).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 12.40 (s,1H,indoleNH); 12.10,(s,1H,indoleNH);11.60(s,1H,imidazoleNH);7.30-8.(m,11H,Ar-H).

LCMS:m/z=417,Analysis:Calcd for: $\text{C}_{23}\text{H}_{14}\text{Cl}_2\text{N}_4$ ,C(66.20); H,(3.38);N,(13.43);

Found:C,66.35; H,3.31; N,13.37 Light yellow crystals..

### Compound 3i

IR (KBr) ( $\lambda_{\text{max}}$  in  $\text{cm}^{-1}$ ): 3419, 3257 (indoleN-H); 3231(imidazole NH)1278(C=N); 2968 (Ar CH stretch).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ (ppm): 12.35(s,1H,indoleNH); 11.50,(s,1H,indoleNH);11.25(s,1H,imidazoleNH);7.36-8.01(m,11H,Ar-H).



LCMS:m/z=396, Analysis:Calcd for:C<sub>24</sub>H<sub>17</sub> Cl N<sub>4</sub> ,C(72.63); H,(4.32);N,(14.12); Found:C,72.55; H,4.35; N,14.03 Light yellow crystals..

### Biological Activity

#### Antimicrobial activity

The antibacterial activities of compounds (**4a-l**), were carried out using Cup plate diffusion method[25]. This method depends on the diffusion of the antibiotic from a cavity through the solidified agar layer in a petri dish to an extent such that the growth of the added microorganism is prevented in a circular zone around the cavity containing a solution of the antibiotic. For antibacterial activity, antibacterial species used are two Gram negative species *Escherichia coli*(ATCC 9637), *Salmonella typhi* (ATCC 6539) and two Gram-positive species *Bacillus subtilis*(ATCC 6633), *Staphylococcus aureus*(ATCC 29737). Two fungal strains *Aspergillus niger* (ATCC 16509), *Aspergillus fumigatus* (ATCC 16406). are used for antifungal activity. Solution of each compound at a concentration of 1000 µg/ml in DMSO was prepared and the inhibition zone diameter in millimeter was used as the criterion for measuring the microbial activity after 24h for bacteria and 72h for fungi. Ciprofloxacin is used as bacterial standards and amphotericin B is used as fungal standards for references. To evaluate the efficacy of the tested compounds under the same conditions. DMSO used as control and solvent to prepare compound solutions. Measurements of results are shown in Table 1

**Table:1**, Antimicrobial activity results of synthesized compounds. Scheme 1

compound	Antibacterial Activity				Antifungal Activity	
	Gram Positive		Gram negative			
	<i>B.Subtilis</i>	<i>S.aureus</i>	<i>E. Coli</i>	<i>S.Typhi</i>	<i>A.fumigatus</i>	<i>A.niger</i>
3a	15±.471	11±.313	14±253268.	14±.	13±.341	12±252.
3b	15±.272	14±.360	13±.27	13±273.	16±.381	16±.135
3c	13±.54	12±256.	12±.15	13±.361	13±227.	11±.272
3d	13±.136	12±.272	13±243.	12±.123	12±.136	13±.361
3e	17±.143	15±163	14±.326	16±.241	16±.341	15±.143
3f	12±.28	13±.362	13±.361	12±14.	12±.272	12±.236
3g	11±.471	10±.271	10±.139	11±.27	10±.213	12±.251
3h	16±.362	16±.136	15±.212	14±.263	17±.361	17±.214
3i	13±272	13±.324	12±.238	12±.153	12±.258	14±.321
Ciproflaxcin	19	21	19	20		

Amphotericin.B					20	20
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Values are expressed in mean $\pm$ SD(n=3)

## RESULTS AND DISCUSSION

### Chemistry

Compounds 2-(2,5-disubstituted-1H-indol-3-yl)-7-substituted-1,4-dihydroimidazo[4,5-b] indole (**3a-I**) are obtained by cyclocondensation of various 2,5-disubstituted indole-3-carboxaldehydes (**2**) with substituted isatin (**1**) using ZrO<sub>2</sub> NPs as catalyst in the presence ammonium acetate under reflux condition heated at 110°C for 30 minutes. The IR spectrum of 2-(5-chloro-2-phenyl-1H-indol-3-yl)-1,4-dihydroimidazo[4,5-b] indole (**3b**) showed characteristic absorption at 3431 cm<sup>-1</sup> and 3251 cm<sup>-1</sup> corresponding to indole NH, absorption at 3224 cm<sup>-1</sup> corresponds to the imidazole NH. The <sup>1</sup>H NMR spectrum of compound **3b** has shown a singlet at down field  $\delta$  11.81(s, 1H, NH) and  $\delta$  11.31(s, 1H, NH) integrating for single proton each due to deshielded indole NH and a singlet at  $\delta$  10.6(s, 1H, NH) integrated for a single proton due to the imidazole NH, which are D<sub>2</sub>O exchangeable. A multiplet from  $\delta$  7.10-8.30 (m, 12H, Ar-H) integrating for twelve aromatic protons. The <sup>13</sup>C NMR Spectrum of **3b** has shown peaks at  $\delta$  151, 149, 147, 142, 141, 134, 133, 132, 131, 127, 124, 119 and 106 integrated for different carbon atoms in the molecule. The most deshielded carbon appeared at  $\delta$  151 is due to imidazole ring carbon (C2) flanked between two nitrogens. The peak at  $\delta$  149 is due to the indole carbon attached to -NH. Peak at  $\delta$  147 is due to carbon flanked between indole -NH and imidazole nitrogen. Peak at  $\delta$  142 is due to 2,5-disubstituted indole carbon attached to -NH.

### Biological activity

All the final synthesized derivatives were taken for preliminary screening to evaluate antibacterial activity by cup plate method, in the nutrient agar medium against two gram positive and two gram-negative bacterial strains at concentration of 1000  $\mu$ g/ml. The zone of inhibition (mm) of each derivative was ascertained and compared with Ciprofloxacin taken as standard drug for anti-bacterial activity. DMSO was used to prepare stock solutions of test compounds. The findings of antibacterial evaluation revealed that most of the compounds have variable activity against bacterial strains. Compounds **3b**, **3e** and **3h** are the active compounds which present excellent activity against the bacteria in comparison to

standard drug Ciproflaxcin **3e** is found to exhibit excellent activity against bacterial strains. All the final compounds were examined for antifungal activity using cup plate method, in the agar medium against two pathogenic fungal strains. The area of inhibition (mm) of each derivative was ascertained and compared with Amphotericin B standard drug. The compounds **3b, 3e and 3h** were found active compounds against the fungal strains used. All the synthesized products were found to be active against *A. fumigatus* than *A. Niger*. However none of the compounds exhibited zone of inhibition more than that of standard.

### Conclusion

ZrO<sub>2</sub>nanoparticles have been synthesized and a novel synthetic route has been developed for the condensation reaction of isatin derivatives with ammonium acetate and substituted indole-3-carboxaldehyde using ZrO<sub>2</sub>nanoparticles under ethanol conditions to yield compound comprising fused two to three heterocycles.. The yields of the products obtained were up to 93% at 110°C. The advantage of the proposed method is its facile reaction conditions; the product can be isolated very easily without the use of column chromatography and the catalyst can be recycled. The obtained catalyst is expected to contribute to the development of environmentally benign methods and forms a part of nanomaterial chemistry.

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