

**Research Article****Synthesis of new Imidazole Derivatives as effective Antimicrobial Agents**Bipin Kumar Verma<sup>1,2\*</sup>, Sunil Kapoor<sup>3</sup>, Umesh Kumar<sup>4</sup>, Savita Pandey<sup>2</sup>, Priti Arya<sup>2</sup><sup>1</sup>Department of Pharmaceutical Science, Bhagwant University, Ajmer, Rajasthan, India<sup>2</sup>Govt Polytechnic, Kashipur, U.S. Nagar, Pin Code-244713, Uttarakhand, India<sup>3</sup>Rexcin lab. Pvt. Ltd. Baddi (H.P), India<sup>4</sup>Department of Pharmaceutical Science, Om bioscience college, Haridwar, Roorkee-247667, Uttarakhand, India**ARTICLE INFO:****Article history:**

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**ABSTRACT**

In the present work, some new imidazole derivatives (**3i-xii**) were synthesized as per design synthetic protocol scheme. The structures of newly prepared compounds were confirmed by modern analytical technique (IR, <sup>1</sup>H-NMR, Mass spectral data) and elemental analysis, results found in full agreement with their assigned structures. All the synthetic compounds were screened for their antimicrobial activity against bacterial strains viz. *Escherichia coli* (*E. coli*, MTCC 2961), *Staphylococcus aureus* (*S. aureus*, MTCC 3160), *Bacillus subtilis* (*B. subtilis*, MTCC 121), *Klebsiella pneumoniae* (*K. pneumoniae*, MTCC 3040) and *Micrococcus luteus* (*M. luteus*, MTCC 7527)) and fungal strains viz. *Candida albicans* (*C. albicans*, MTCC 227), *Aspergillus niger* (*A. niger*, MTCC 277) and *Aspergillus flavus* (*A. flavus*, MTCC 418); results showed good to remarkable activity. The MIC (minimum inhibitory concentration) values were determined by comparison to ciprofloxacin (anti-bacterial) and fluconazole (anti-fungal) as standard drug. Among them, compound **3iv** and **3x** exhibited notable antimicrobial activity. These compounds may be used as new template for the searching of potential antimicrobial agents.

**Introduction**

The main aim of medicinal chemist in the recent times has been to develop drugs with enhanced their efficacy and duration of action and by decreasing their toxicities and side effects as well as creating new drugs by molecular modification [1-2]. The pharmaceutical industry and specifically, a medicinal chemist have continued commitment towards this drug development. The organic medicinal substances can be of natural or synthetic origin. The synthetic drugs are prepared by modifications of the structures of natural drugs, or by pure synthesis [3-4]. Over the years, innovations in new drug therapy has become, more complex, time consuming, costly, and the practicing medicinal chemists have been bombarded with surplus new methods and technologies to make the job of drug discovery more efficient [5]. The heterocyclic ring comprises the core of the active moiety or pharmacophore. By far the most numerous and most important heterocyclic systems are those of five and six membered ring. For example, pyrazoles, imidazoles, triazoles, thiadiazoles, triazolo-thiadiazoles, oxadiazoles, isoxazoles, isothiazole, oxazoles, thiazoles etc. Imidazoles are a class of

five membered heterocyclic compounds having two nitrogen and three carbon atoms. Imidazole is an important group of compounds reported to have different biological activities and the present study was undertaken in order to synthesize some new derivatives of imidazole and related fused heterocyclic compounds and screen for their antimicrobial activity [6-12]. The infections of systemic bacterial and fungal has been increasing serious and growing threatens to human health over the past few decades. Currently present potent antimicrobial agents for the management of infections may develop microbial resistance to existing drugs a major concern in antimicrobial therapy and many compounds have been synthesized with this aim but their clinical use has been limited by their relatively high risk of toxicity, microbial resistance and pharmacokinetic deficiencies. Among the various classes of heterocyclic compounds, imidazole is an important component of pharmacologically active compounds and a part of various available marketed drugs like Azathioprine (Leukemia), Metronidazole (Protozoal and antimicrobial activity, trichomoniasis, amoebiasis and

giardiasis), Dacarbazine (Hodgkin's disease), Tinidazole (Metronidazole), Ornidazole (Antiprotozoal and antibacterial activity), Satranidazole (C 10213 Go), (Trichomoniasis and amoebiasis), Cimetidine (Duodenal and gastric ulcers), Carbimazole (Thyroid disorders), Tolazoline (Vasodilator action), Naphazoline (Vasoconstrictor), Tetrahydrozoline (Vasoconstrictor) [12-15]. Recent studies have been revealed that the substituted imidazole derivatives attracted attention due to their broad spectrum of pharmacological activities such as anti-inflammatory, analgesic, antimicrobial, antiviral, antifungal, antibacterial, anti-tubercular, anti-cancer, anti-hypertensive, anti-obesity and anti-convulsant [15-16]. In the present studies it has been thought to synthesize newer imidazole derivatives and the structures of the synthesized compounds confirmed on the basis of their elemental analysis and modern analytical techniques such as IR, <sup>1</sup>H-NMR and Mass spectral data results.

### Experimental Protocol

#### General materials and instrumentations

All the chemicals and solvent procured from E. Merck and S. D. Fine chemicals (India). Melting points were determined by open tube capillary method and are uncorrected. Thin layer chromatography (TLC) plates prepared by silica gel G were used to monitor the reaction as well as to confirm the purity of the compound by using solvent systems as toluene: ethyl acetate: formic acid (5:4:1), benzene: acetone (9:1) were used to run the TLC. The spots were visualized under iodine vapours/UV light. IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer using KBr Pellets. <sup>1</sup>H-NMR spectra were recorded on DPX-300 and BRUKER-400 Ultra Shield™ NMR spectrometer, using TMS as internal standard in CDCl<sub>3</sub>/DMSO-d<sub>6</sub>. Microanalysis of the compounds was done on Perkin-Elmer model 240 analyzer and the values were found within ±0.4% of the theoretical values. Mass spectrometry was recorded on LC-MS/MS (WATERS, mass lyns version 4.1) spectrometer.

#### Synthesis

The compounds of the synthetic protocol scheme were obtained in the following steps

**Synthesis of 1-(Biphenyl-4-yl) ethanone (1):** The starting material biphenyl ethanone (1) was prepared by heating biphenyl with anhydrous AlCl<sub>3</sub> in presence of CS<sub>2</sub> and acetic anhydride. The usual work up of the reaction mixture followed by recrystallized from ethanol gave pure compound. The purity of the compound was verified with the help of TLC (B: A, 9 : 1). Percentage yield was found 85% and noted Mp.158-160°C. IR spectra are very informative and provided evidence for the formation of the expected structures.

**Synthesis of 2-(Biphenyl-4-yl)-2-oxoacetaldehyde (2):** Compound 2-(Biphenyl-4-yl)-2-oxoacetaldehyde (2) was synthesized from biphenyl ethanone (1) in presence of selenium dioxide, usual work up of the reaction mixture gave a yellow liquid which was found pure on TLC examination (TEF 5: 4: 1). The structure of compound was confirmed on the basis of spectral studies.

**General procedure for synthesis of 4-(Biphenyl-4-yl)-2-(substituted phenyl)-1H-imidazole (3i-xii):** Biphenyl-2-oxoacetaldehyde (2) was refluxed with different aromatic aldehyde in presence of ammonium acetate and glacial acetic acid. The usual work up of the reaction mixture followed by recrystallized from acetone to get the desired products (3i-xii). The structures of compounds were confirmed on the basis of their IR and <sup>1</sup>H-NMR spectral studies. The compound was found pure on TLC examination (BA 9: 1) and (TEF 5: 4: 1) and its spectral data was found satisfactory for the proposed structures.

**Synthesis of 4-(biphenyl-4-yl)-2-phenyl-1H-imidazole (3i):** Yield: 70%, Mp: 134-137°C, Rf = 0.53. IR (KBr, cm<sup>-1</sup>): 3450(C-H, N-H), 3041(C-H, Ar-H), 2871(C-H, CH<sub>2</sub>), 1595(C=N), 1564 (C=C). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ, ppm): 10.93 (H, s, N-H), 6.53-8.79 (H, m, Ar-H), 7.92 (1H, s, CH, imidazole). ESI-MS (m/z): 296 (M+). Anal.calcd. for C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>: C, 65.11; H, 5.44; N, 9.45. Found: C, 75.11; H, 4.44; N, 9.51.

**Synthesis of 4-(4-(biphenyl-4-yl)-1H-imidazol-2-yl)phenol (3ii):** Yield: 75%, Mp: 151-154°C, Rf = 0.54. IR (KBr, cm<sup>-1</sup>): 3397(C-H, N-H), 3213(OH), 3035(C-H, Ar-H), 2931(C-H, CH<sub>2</sub>), 1675(C=N), 1556 (C=C). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ, ppm): 10.51 (H, s, N-H), 8.01-6.79 (H, m, Ar-H), 9.01 (1H, s, CH, imidazole), 9.46 (H, s, OH). ESI-MS (m/z): 312 (M+). Anal.calcd. for C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>O: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.79; H, 4.11; N, 8.95.

**Synthesis of 4-(biphenyl-4-yl)-2-(3-chlorophenyl)-1H-imidazole (3iv):** Yield: 77%, Mp: 148-151°C, Rf = 0.47. IR (KBr, cm<sup>-1</sup>): 3405(C-H, N-H), 3021(C-H, Ar-H), 2947(C-H, CH<sub>2</sub>), 1623(C=N), 1564 (C=C), 733(C-Cl). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ, ppm): 9.97 (H, s, N-H), 7.85-6.59 (H, m, Ar-H), 8.93 (1H, s, CH, imidazole). ESI-MS (m/z): 330 (M+). Anal.calcd. for C<sub>21</sub>H<sub>15</sub>ClN<sub>2</sub>: C, 76.24; H, 4.57; N, 8.47. Found: C, 76.27; H, 4.54; N, 8.37.

**Synthesis of 3-(4-(biphenyl-4-yl)-1H-imidazol-2-yl)phenol (3v):** Yield: 64%, Mp: 132-133°C, Rf = 0.53. IR (KBr, cm<sup>-1</sup>): 3451(C-H, N-H), 3267(OH), 3058(C-H, Ar-H), 2879(C-H, CH<sub>2</sub>), 1578(C=N), 1551 (C=C). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ, ppm): 10.23 (H, s, N-H), 7.95-6.73 (H, m, Ar-H), 8.31 (1H, s, CH, imidazole), 9.37 (H, s, OH). ESI-MS (m/z): 312 (M+). Anal.calcd. for C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>O: C, 64.75; H, 5.16; N, 8.97. Found: C, 60.79; H, 5.21; N, 8.95.

**Synthesis of 4-(biphenyl-4-yl)-2-(4-chlorophenyl)-1H-imidazole (3vi):** Yield: 72%, Mp: 185-187°C, Rf = 0.47. IR (KBr, cm<sup>-1</sup>): 3379(C-H, N-H), 3086(C-H, Ar-H), 2951(C-H, CH<sub>2</sub>), 1663 (C=N), 1491(C=C), 719(C-Cl). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ, ppm): 9.73 (H, s, N-H), 7.89-6.57 (H, m, Ar-H), 9.11(1H, s, CH, imidazole). ESI-MS (m/z): 330 (M+). Anal.calcd. for C<sub>21</sub>H<sub>15</sub>ClN<sub>2</sub>: C, 55.30; H, 4.61; N, 15.71. Found: C, 55.41; H, 4.75; N, 15.92.

**Synthesis of 4-(biphenyl-4-yl)-2-(4-bromophenyl)-1H-imidazole (3vii):** Yield: 81%, Mp: 142-145°C, Rf = 0.57. IR (KBr, cm<sup>-1</sup>): 3447(C-H, N-H), 3171 (C-H, Ar-H), 2817 (C-H, CH<sub>2</sub>), 1652 (C=N), 1539 (C=C), 803 (C-Br). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ, ppm): 10.01 (H, s, N-H), 7.91-6.85 (H, m, Ar-H), 8.71 (1H, s, CH, imidazole). ESI-MS (m/z): 375 (M+).

Anal.calcd. for C<sub>21</sub>H<sub>15</sub>BrN<sub>2</sub>: C, 57.21; H, 4.03; N, 7.47. Found: C, 56.79; H, 4.07; N, 7.51.

**Synthesis of 4-(biphenyl-4-yl)-2-(4-methoxyphenyl)-1H-imidazole (3x):** Yield: 71%, Mp: 160-163°C, Rf = 0.63. IR (KBr, cm<sup>-1</sup>): 3031(C-H, Ar-H), 2905(C-H, CH<sub>2</sub>), 1662(C=N), 1571 (C=C). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ, ppm): 9.97 (H, s, N-H), 7.85-6.21 (H, m, Ar-H), 9.03 (1H, s, CH, imidazole), 3.85 (H, s, OCH<sub>3</sub>). ESI-MS (m/z): 326 (M<sup>+</sup>). Anal.calcd. for C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O: C, 68.91; H, 5.56; N, 8.51. Found: C, 68.79; H, 5.51; N, 8.58.

**Synthesis of 3-(4-(biphenyl-4-yl)-1H-imidazol-2-yl) phenol (3xi):** Yield: 78%, Mp: 140-143°C, Rf = 0.55. IR (KBr, cm<sup>-1</sup>): 3421(C-H, N-H), 3307(OH), 3041(C-H, Ar-H), 2867(C-H, CH<sub>2</sub>), 1571(C=N), 1543 (C=C). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ, ppm): 10.11 (H, s, N-H), 7.89-6.68 (H, m, Ar-H), 8.73 (1H, s, CH, imidazole), 9.31 (H, s, OH). ESI-MS (m/z): 312 (M<sup>+</sup>). Anal.calcd. for C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>O: C, 55.45; H, 5.19; N, 9.13. Found: C, 55.51; H, 5.21; N, 9.21.

**Synthesis of 4-(biphenyl-4-yl)-2-(4-fluorophenyl)-1H-imidazole (3xii):** Yield: 67%, Mp: 171-175 °C, Rf = 0.45. IR (KBr, cm<sup>-1</sup>): 3127(C-H, Ar-H), 2945(CH<sub>2</sub>), 1635(C=N), 1589(C=C), 861 (C-F). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, δ, ppm): 11.01 (H, s, N-H), 8.11-7.23 (H, m, Ar-H), 9.25 (1H, s, CH, imidazole). ESI-MS (m/z): 314 (M<sup>+</sup>). Anal.calcd. for C<sub>21</sub>H<sub>15</sub>FN<sub>2</sub>: C, 52.35; H, 4.81; N, 8.91. Found: C, 53.21; H, 4.93; N, 8.97.

#### Antimicrobial Evaluation

The inhibition of microbial growth under standardized condition may be utilized for demonstrating the therapeutic efficacy of any subtle change in the antibiotic molecule. Which may not be detected by chemical method will be revealed by a reduction in the anti-microbial activity and hence microbiological assays are very useful for resolving doubts regarding possible loss of potency of antibiotics and their preparations of the antibiotic having a known activity. The in-vitro antibacterial and antifungal activities of the synthesized compounds were carried out by microdilution susceptibility test using cup-plate technique. Antibacterial activity of newly synthesized compounds (3i-xii) was screened against bacterial strains viz. *Escherichia coli* (*E. coli*, MTCC 2961), *Staphylococcus aureus* (*S. aureus*, MTCC 3160), *Bacillus subtilis* (*B. subtilis*, MTCC 121), *Klebsiella pneumoniae* (*K. pneumoniae*, MTCC 3040) and *Micrococcus luteus* (*M. luteus*, MTCC 7527). The anti-fungal activity was screened against fungal strains viz. *Candida albicans* (*C. albicans*, MTCC 227), *Aspergillus niger* (*A. niger*, MTCC 277) and *Aspergillus flavus* (*A. flavus*, MTCC 418). The MIC (minimum inhibitory concentration) values were determined in compare to standard drug Ciprofloxacin (anti-bacterial) and Fluconazole (anti-fungal). The MIC is considered to be the lowest drug concentration for which there is no microbial growth.

#### Antibacterial Activity

##### Experimental Procedure

In-vitro antibacterial activity of the synthesized compounds was tested by disc diffusion method under standard condition

using Muller Hinton Agar medium. The test organisms were first cultured in Nutrient broth and incubated for 24 hrs at 37°C and then freshly prepared bacterial cells were spread onto the Muller Hinton agar plates in a laminar flow cabinet. The test compounds which were previously dissolved in DMSO were then soaked onto sterile discs of Whatman filter paper no. 1 (6 mm diameter). The discs were then placed onto the surface of the previously prepared inoculated plates and incubated. After 24 hrs of incubation at 37°C, the diameter of zone of inhibition was measured for each compound in mm. The activity was compared with standard antibiotic ciprofloxacin (positive control) and a disc impregnated with dimethylsulfoxide (DMSO) was used as a negative control [18-19]. All the tests were performed in triplicate and the average was taken as final reading. Compounds which have shown good zone of inhibition were selected for minimum inhibitory concentration (MIC) determination.

#### Antifungal activity

##### Experimental Procedure

In-vitro antifungal activity of the synthesized compounds was tested by disc diffusion method under standard conditions using Potato dextrose agar medium. Sterile discs of Whatman filter paper no.1 (6 mm diameter) containing specific amounts of an antifungal agent fluconazole (300 mg for the synthesized compounds) were placed on the surface of an agar plate inoculated with a standardized suspension of the microorganisms tested. The plates were incubated at 28±2°C for 72 hrs for evaluating antifungal activity. A paper disc impregnated with dimethylsulfoxide (DMSO) was utilized as negative control [19-20]. The nutrient agar medium was prepared and autoclaved at 15 lbs pressure for 20 minutes and this media was poured into petri plates and was allowed to solidify. On the surface of media microbial suspension was spread with the help of sterilized cotton swab. Cups were made by boring into agar surface with a previously sterilized cork borer and scooping out the punched part of agar. Four cavities or cups were made in the medium and different concentrations of the test compounds and standard drug Fluconazole were poured in these cavities. The plates were kept at room temperature for 1 hr and then incubated at 37±0.5 °C for 24 hrs. The diameter of the zone of inhibition formed around the cavities (cups) after 24 hrs incubation was measured and percentage inhibition of the compound were evaluated. A solvent control was also run to know the activity of the blank.

#### Determination of MIC

MIC of the compound was determined by agar streak dilution method. A stock solution of the synthesized compounds (100 µg/mL) in DMSO was prepared and graded quantities of the test compounds were incorporated in specified quantity of molten sterile agar (Muller Hinton agar). A specified quantity of the medium (40-50°C) containing the compound was poured into a Petri dish to give a depth of 3-4 mm and allowed to solidify. Suspension of the micro-organism was prepared to contain approximately 10<sup>5</sup> cfu/mL and applied to plates with serially diluted compounds in DMSO to be tested and incubated at 37°C. At the end of the incubation period, the

MIC values were determined. All determinations were done in triplicates and the average was taken as final reading. The standard antibiotic, ciprofloxacin (100 µg/mL) used as positive control and 100 mL of DMSO used as a negative control. The MIC was considered to be the lowest concentration of the test substance exhibiting no visible growth of bacteria or fungi on the plate [25-26].

## Result and Discussion

### Chemistry

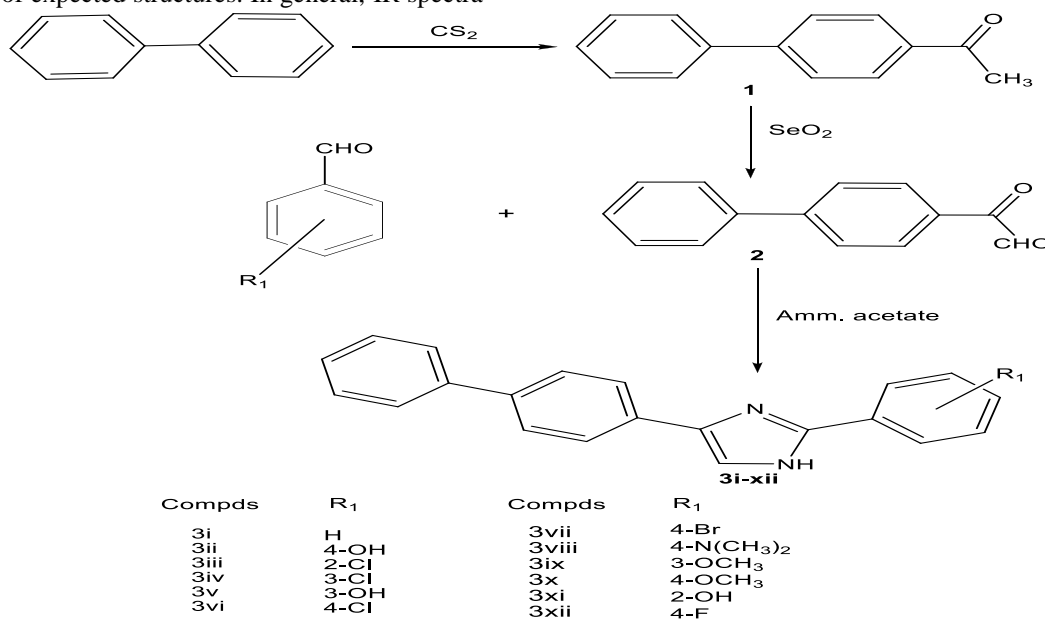
The title compounds (3i-xii) were synthesized as per synthetic scheme outline. In this scheme biphenyl ethanone (1; starting material) was treated with selenium dioxide to get 2-(biphenyl-4-yl)-2-oxoacetaldehyde (2). Compound 2 was refluxed with different aromatic aldehydes in presence of ammonium acetate and glacial acetic acid, followed by treatment with chlorobenzene in THF to get twelve new imidazole derivatives (3i-xii). The structures of newly prepared compounds were established on the basis of modern analytical techniques (FT-IR, <sup>1</sup>H-NMR and mass spectral data) and elemental analysis. The final compounds were purified by recrystallization with suitable solvent and found pure on TLC examination.

### Structural investigations

The starting material 1-(biphenyl-4-yl) ethanone (biphenyl ethanone, 1) was prepared by heating biphenyl with anhydrous AlCl<sub>3</sub> in the presence of CS<sub>2</sub> and acetic anhydride. The usual work up of the reaction mixture followed by recrystallized from ethanol gave pure compound. The purity of the compound was verified with the help of TLC (B: A, 9:1). % age of yield was found 83% and melting point noted 151-152°C. IR spectra are very informative and provided evidence for the formation of expected structures. In general, IR spectra

of acetophenone showed a strong band at 1673 cm<sup>-1</sup> for the confirmation of C=O. Whereas <sup>1</sup>H-NMR further confirmed the structure due to the presence of a singlet of CH<sub>3</sub> at 2.61 ppm.

Compound 2 [2-(biphenyl-4-yl)-2-oxoacetaldehyde] was synthesized from 1-(biphenyl-4-yl) ethanone (1) in the presence of selenium dioxide and after work out of reaction gave a yellow liquid which was found pure on TLC examination (TEF 5: 4: 1). The structure of compound was confirmed on the basis of spectral studies. In IR spectra showed a band at 2851 cm<sup>-1</sup> for the confirmation of aldehydic C-H stretching was very clear. The <sup>1</sup>H-NMR spectra left no doubt with a singlet of aldehydic proton at 9.810 ppm. Compound 2 [2-(biphenyl-4-yl)-2-oxoacetaldehyde] was refluxed with different aromatic aldehyde in the presence of ammonium acetate and glacial acetic acid. The usual work up of the reaction mixture followed by recrystallized from acetone to get the desired products (3i-xii). The compound was found pure on TLC examination (TEF 5: 4: 1) and its spectral data was found satisfactory for the proposed structures. The structure of this compound was confirmed on the basis of their IR and <sup>1</sup>H-NMR spectral studies. In IR spectral studies, the compounds showed intense bands in the region 1535-1633 cm<sup>-1</sup> of C=N stretching due to the ring closure. In addition, the absorption bands at 1351-1367 cm<sup>-1</sup> are attributed to the C-N stretching vibrations, which also confirm the formation of desired imidazole ring in the compounds. Whereas <sup>1</sup>H-NMR spectra further confirm the structure due to disappearance of the peak of aldehydic proton and appearance of a single peak of NH (imidazole ring) at 11.23 ppm due to ring closure.



Scheme: Synthetic protocol.

## Evaluation of Anti-microbial Screening

The synthetic compounds were prepared retaining the functional groups responsible for anti-microbial activity and



tested in-vitro against representatives of Gram positive and Gram negative bacteria as well as fungi. It was found that the synthesized compounds were more effective against the Gram-positive bacteria when compared to Gram-negative bacteria. It is believed that the strong lipophilic character of the molecule play an essential role in producing antimicrobial effect. The lipophilicity (hydrophobicity) of a compound is an important physical property that influences membrane permeation, dissolution rate and bioavailability of compounds which is a primary factor in controlling the interaction of drugs with biological systems. The lipophilicity of a compound may be expressed in terms of log P, which is considered to be very important factor for prediction of antimicrobial activity [21-22]. The octanol/water partition coefficient  $C \log P$  is a measure of hydrophobicity/ lipophilicity. Furthermore, it is a crucial factor governing passive membrane partitioning, influencing permeability (i.e. increasing logP enhances permeability). Drugs with high partition coefficients (hydrophobic) are preferentially distributed to lipophilic compartments such as lipid bilayers of cells while hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as blood serum. The values of  $C \log P$  were calculated using Chem Draw Ultra 8.0 software integrated with Cambridge Software (Cambridgesoft Corporation) obtained results shown in Table 1. Molar refractivity (MR), the measure of steric factor, bulkiness of the molecule and its polarizability [23-24] was also calculated using Chem Draw Ultra 8.0 software integrated with Cambridge Software (Cambridgesoft Corporation) to explain the activity behavior of the synthesized compounds and obtained results showed in Table 1. Molar refractivity is the molar volume corrected by the refractive index. It has been inferred after the correlation of the antimicrobial data with the values of  $C \log P$  and molar refractivity; the compounds having greater values of  $C \log P$  and molar refractivity showed better antimicrobial activity. The permeability of the membrane of the bacteria plays an important role for the determination of

antibacterial activity. The antibacterial activity of the compounds may be related to cell wall structure of the bacteria. This is possible because the cell wall is essential for the survival of many bacteria and some antibiotics are able to kill bacteria by inhibiting a step in the peptidoglycan synthesis. Gram negative bacteria have a relatively thin cell wall consisting of a few layers of peptidoglycan surrounded by a second lipid membrane containing lipopoly sachharides and lipoproteins. In contrast Gram positive bacteria possess a thick cell wall containing many layers of peptidoglycan and teichoic acids. These differences in cell wall structure can produce differences in the antibacterial susceptibility and some antibiotics which are effective against Gram-positive bacteria are found to be ineffective against Gram negative bacteria [21-23].

#### Structural activity relationship

Furthermore the outer membrane of the Gram-negative bacteria is less permeable than the cell wall of Gram positives. Therefore synthesized compounds may have shown better antibacterial activity towards Gram positive bacteria than Gram-negatives. On the basis of obtained result the following observations could be made that: Compounds (3iv), (3viii) and (3x) was the most potent compound of the series suggesting that it may be due to the highest value of log P and molar refractivity. In general substitution with electron releasing group at any position in either of the hydroxyl (3ii), N-dimethy (3viii) or methoxy (3ix & 3x) series has constant  $C \log P$  value of its analogues. Substitution with OCH<sub>3</sub> group at the ortho position showed different  $C \log P$  values in both series. In phenoxy series  $C \log P$  value is decreased as compare to its para analogue due to the reason that OCH<sub>3</sub> group being a bulky molecule with oxygen as its part produces repulsion as well as steric hindrance. Therefore Compound (3x) having p-OCH<sub>3</sub> group is more active than (3ix) having m-OCH<sub>3</sub> group. This indicated that substitution at para position enhanced the antibacterial activity.

**Table 1: Compounds code, Substituted (-R1), log P and molar refractivity of title compounds (3i-xii).**

Compd.	Subs. (-R)	C log P	Molar Refractivity
3i	H	3.91	89.81
3ii	4-OH	5.83	113.70
3iii	2-Cl	4.45	112.80
3iv	3-Cl	6.31	114.63
3v	3-OH	5.95	107.79
3vi	4-Cl	5.27	113.01
3vii	4-Br	5.91	109.35
3viii	4-N(CH <sub>3</sub> ) <sub>2</sub>	6.03	112.13
3ix	3-OCH <sub>3</sub>	5.73	113.17
3x	4-OCH <sub>3</sub>	6.73	113.51
3xi	2-OH	6.21	112.67
3xii	4-F	5.58	109.63

**Anti-bacterial activity**

The results of anti-bacterial screening of all the newly synthesized compounds are showed in Table 2 and 3. Compound 3iv [4-(biphenyl-4-yl)-2-(3-chlorophenyl)-1H-imidazole] and compound 3x [4-(biphenyl-4-yl)-2-(4-methoxyphenyl)-1H-imidazole] showed notable activity against *E. coli*, *B. subtilis* and *K. pneumoniae*. Some of them showed moderate activity and others rest good activity.

Compounds (3ii, 3viii & 3ix) were shown moderate activity against *E. coli*, *S. aureus*, *M. luteus* and *K. pneumoniae*, whereas compounds (3iii, 3vii, 3xi & 3xii) showed mild activity against few bacterial strains. Results of the antibacterial activity shown in Table 2 as zone of inhibition and Table 3 as percentage inhibition against various bacterial strains, while maximum activity was observed at 100 µg/mL.

**Table 2: Antibacterial activity measure by zone of inhibition of title compounds (3i-xii)**

Compd.	<i>E. coli</i> (MTCC-1687)		<i>S. aureus</i> (MTCC-2940)		<i>B. subtilis</i> (MTCC- 441)		<i>M. luteus</i> (MTCC 7527)		<i>K.pneumonia</i> (MTCC 3040)	
	50 µg/mL ± SD <sup>b</sup>	100 µg/ mL ± SD	50 µg/ mL ± SD	100 µg/ mL ± SD	50 µg/mL ± SD	100 µg/ mL ± SD	50 µg/ mL ± SD	100 µg/ mL±SD	50 µg/ mL ± SD	100 µg/ mL±SD
3i	8.11 ± 2.35	14.01 ± 2.01	nt	nt	8.32 ± 0.58	9.20 ± 1.32	10.31 ± 1.58	9.31 ± 1.1	11.30 ± 0.51	12.31 ± 1.15
3ii	14.13 ± 1.71	16.78 ± 1.21	15.61 ± 1.51	17.21 ± 2.51	13.21 ± 1.31	14.21 ± 1.32	14.47 ± 1.32	17.17 ± 1.44	15.41 ± 1.31	18.51 ± 1.37
3iii	12.17 ± 3.26	13.58 ± 1.27	nt	nt	13.51 ± 1.37	15.72 ± 2.32	nt	nt	12.31 ± 1.31	17.31 ± 1.13
3iv	20.31 ± 1.51	23.53 ± 1.23	14.18 ± 1.32	16.87 ± 1.17	19.17 ± 1.16	21.97 ± 0.67	15.21 ± 1.23	16.54 ± 1.18	18.13 ± 1.15	20.53 ± 2.13
3v	15.13 ± 1.33	17.37 ± 1.04	13.17 ± 1.12	14.65 ± 1.71	14.64 ± 1.52	15.61 ± 1.12	13.61 ± 1.53	15.67 ± 0.58	14.22 ± 1.36	14.61 ± 1.13
3vi	14.17 ± 1.12	16.31 ± 1.51	14.61 ± 1.45	15.23 ± 2.53	16.6 ± 1.73	15.21 ± 1.25	11.67 ± 1.53	18.31 ± 1.12	nt	nt
3vii	16.23 ± 2.35	15.31 ± 1.53	nt	nt	15.47 ± 1.23	17.68 ± 1.51	17.21 ± 1.00	18.21 ± 1.01	15.01 ± 1.17	17.12 ± 1.11
3viii	16.15 ± 1.13	17.36 ± 2.31	15.61 ± 1.45	16.23 ± 2.51	14.61 ± 1.53	15.31 ± 1.11	15.17 ± 1.39	17.61 ± 0.21	14.37 ± 1.13	16.89 ± 0.55
3ix	14.15 ± 1.11	16.36 ± 1.33	15.17 ± 1.21	16.33 ± 1.11	13.23 ± 1.13	14.83 ± 1.53	15.93 ± 1.15	17.31 ± 1.27	14.31 ± 1.13	15.17 ± 1.25
3x	18.15 ± 1.41	21.61 ± 1.03	15.11 ± 0.5	17.21 ± 1.23	17.01 ± 1.31	19.61 ± 1.41	15.16 ± 1.51	14.61 ± 2.13	17.81 ± 1.32	20.61 ± 1.16
3xi	nt	nt	13.61 ± 1.05	15.61 ± 1.33	11.51 ± 1.72	13.12 ± 1.51	9.61 ± 1.15	11.67 ± 2.36	nt	nt
3xii	11.68 ± 1.15	15.51 ± 1.67	11.23 ± 2.07	14.61 ± 1.57	12.33 ± 1.32	14.61 ± 1.51	nt	nt	15.11 ± 1.05	14.58 ± 2.11
Cipro.	27.51 ± 1.21	29.11 ± 1.17	29.31 ± 1.41	30.37 ± 1.71	28.45 ± 1.51	29.81 ± 1.61	28.33 ± 1.53	30.17 ± 1.11	29.41 ± 1.41	30.17 ± 1.35

Measure zone of inhibition in millimeter, SD; Standard Deviation, Compd.; Compounds, Cipro; Ciprofloxacin, nt; means not tested compounds.

**Table 3: Antibacterial activity as percentage inhibition of title compounds (3i-xii)**

Compd	<i>E. coli</i> (MTCC-1687)		<i>S. aureus</i> (MTCC-2940)		<i>B. subtilis</i> (MTCC- 441)		<i>M. luteus</i> (MTCC 7527)		<i>K. pneumonia</i> (MTCC 3040)	
	50µg/ mL ± SD	100 µg/ mL±SD	50 µg/ mL± SD	100 µg/ mL± SD	50 µg/ mL ± SD	100 µg/ mL± SD	50 µg/ mL± SD	100 µg/ mL± SD	50 µg/ mL± SD	100 µg/ mL±SD
3i	40.83 ± 2.21	51.31 ± 3.41	nt	nt	44.81 ± 3.26	65.19 ± 3.45	61.41 ± 2.72	38.51 ± 5.71	43.15 ± 4.01	39.61 ± 3.46
3ii	61.32 ± 4.31	65.52 ± 5.43	60.27 ± 5.46	54.67 ± 3.53	51.23 ± 1.74	54.36 ± 6.21	57.83 ± 5.42	56.41 ± 6.27	62.31 ± 4.27	59.61 ± 4.41
3iii	68.27 ± 4.21	64.71 ± 5.31	nt	nt	59.71 ± 4.94	66.11 ± 1.23	nt	nt	57.29 ± 3.21	64.31 ± 3.82
3iv	67.11 ± 2.91	57.25 ± 3.62	48.62 ± 3.27	44.81 ± 2.61	64.27 ± 2.51	50.31 ± 3.91	65.81 ± 3.15	61.72 ± 1.63	58.11 ± 2.75	51.26 ± 5.61
3v	45.13 ± 5.21	40.61 ± 5.14	39.01 ± 1.91	38.43 ± 2.21	41.41 ± 4.21	35.77 ± 2.81	47.26 ± 5.20	55.39 ± 2.71	51.05 ± 4.31	40.63 ± 5.21
3vi	55.41 ± 3.41	48.62 ± 3.75	40.41 ± 5.61	61.18 ± 4.10	32.01 ± 4.62	37.51 ± 4.58	36.21 ± 5.63	40.21 ± 4.41	nt	nt
3vii	40.10 ± 4.77	48.52 ± 3.70	nt	nt	45.86 ± 3.01	48.29 ± 6.91	57.11 ± 4.94	53.51 ± 1.65	44.63 ± 4.77	51.51 ± 3.71

3viii	61.78 ± 4.33	57.22 ± 2.83	48.52 ± 2.01	45.96 ± 1.47	53.52 ± 2.01	47.96 ± 1.47	61.31 ± 3.82	57.71 ± 2.50	50.62 ± 4.32	45.21 ± 2.35
3ix	59.31 ± 1.21	56.81 ± 5.26	53.94 ± 2.73	50.61 ± 3.37	51.03 ± 2.53	56.86 ± 7.73	64.66 ± 4.60	57.44 ± 4.44	58.85 ± 3.12	60.84 ± 7.36
3x	60.31 ± 1.21	58.81 ± 5.26	48.48 ± 2.06	51.21 ± 3.66	65.51 ± 4.42	63.67 ± 2.79	59.94 ± 5.62	55.61 ± 1.32	69.39 ± 3.26	64.83 ± 4.24
3xi	nt	nt	58.10 ± 5.61	50.12 ± 1.61	68.05 ± 1.61	60.76 ± 7.17	53.05 ± 3.55	51.04 ± 5.71	nt	nt
3xii	48.01 ± 6.11	58.32 ± 6.51	50.61 ± 5.78	47.94 ± 3.44	52.47 ± 2.11	54.16 ± 2.90	nt	nt	48.17 ± 5.13	58.31 ± 5.61
Cipro.	100.00 ± 1.41	100.00 ± 1.52	100.00 ± 1.65	100.00 ± 2.37	100.00 ± 1.15	100.00 ± 3.45	100.00 ± 1.63	100.00 ± 4.21	100.00 ± 5.89	100.00 ± 2.41

Measure zone of inhibition in percentage inhibition, SD; Standard Deviation, Compd.; Compounds, Cipro; Ciprofloxacin, nt; means not tested compounds

#### Anti-fungal activity

The results of anti-fungal screening of all the newly synthesized compounds are presented in Table 4 and 5. Compound 3iv [4-(biphenyl-4-yl)-2-(3-chlorophenyl)-1H-imidazole] and compound 3x [4-(biphenyl-4-yl)-2-(4-methoxyphenyl)-1H-imidazole] were shown notable activity against *E. coli*, *B. subtilis* and *K. pneumoniae*. Some of them showed moderate activity and others rest good activity. Compounds (3ii, 3viii & 3ix), showed moderate activity against *E. coli*, *S. aureus*, *M. luteus* and *K. pneumoniae*, while compounds (3iii, 3vii, 3xi & 3xii) showed mild activity against few bacterial strains.

The compounds of electron releasing imidazole derivatives (3ii, 3iv, 3viii, 3ix, 3x & xi) presented comparatively better anti-fungal activity than the compounds of electron withdrawing imidazole derivatives (3iii, 3vii & 3xii). Regarding the overall anti-fungal activity was found to be the most potent compound having meta substituted chloro group attached to the aromatic ring and methoxy group on para position. Some of the synthesized compounds tested were endowed with a medium activity against *A. flavus*. Results of the antifungal activity are reported in Table 4 as zone of inhibition and Table 5 as percentage inhibition against various fungal strains, while maximum activity was observed at 100 µg/ml.

**Table 4: Antifungal activity as zone of inhibition of title compounds (3i-xii)**

Compd.	<i>C. albicans</i> (MTCC-3617)		<i>A. niger</i> (MTCC-281)		<i>A. flavus</i> (MTCC 418)	
	50 µg/mL ± SD	100 µg/mL ± SD	50 µg/mL ± SD	100 µg/mL ± SD	50 µg/mL ± SD	100 µg/mL ± SD
3i	15.67 ± 1.53	18.31 ± 1.54	15.67 ± 1.52	19.23 ± 1.08	16.54 ± 1.23	19.13 ± 2.01
3ii	17.12 ± 2.41	19.63 ± 1.21	19.71 ± 1.56	20.19 ± 1.61	19.67 ± 1.53	21.81 ± 1.64
3iii	11.61 ± 1.52	19.17 ± 2.26	17.67 ± 1.52	16.33 ± 1.01	nt	nt
3iv	16.21 ± 1.63	18.73 ± 1.08	19.50 ± 1.12	22.67 ± 1.57	21.50 ± 1.32	23.61 ± 1.53
3v	nt	nt	16.00 ± 1.00	14.31 ± 1.54	15.03 ± 1.42	16.32 ± 1.53
3vi	20.61 ± 1.04	24.21 ± 1.14	21.67 ± 1.08	21.31 ± 1.31	23.67 ± 2.08	13.33 ± 2.53
3vii	14.67 ± 1.63	22.04 ± 1.55	13.33 ± 1.53	16.01 ± 1.06	11.33 ± 1.33	18.56 ± 1.21
3viii	17.31 ± 1.34	19.09 ± 4.65	14.61 ± 1.53	18.83 ± 1.23	21.67 ± 1.51	22.39 ± 1.04
3ix	16.67 ± 2.51	15.31 ± 2.53	16.60 ± 1.53	15.31 ± 2.08	nt	nt
3x	17.13 ± 1.04	19.31 ± 1.53	16.01 ± 1.07	19.36 ± 1.53	18.21 ± 1.22	20.31 ± 1.53
3xi	19.63 ± 3.53	22.20 ± 1.21	13.33 ± 2.51	16.43 ± 1.12	11.31 ± 1.54	17.01 ± 1.32
3xii	nt	nt	16.61 ± 1.15	15.81 ± 1.04	15.61 ± 1.47	16.81 ± 1.01
Fluco.	31.23 ± 1.14	31.81 ± 1.72	30.17 ± 1.32	31.23 ± 1.21	28.56 ± 2.51	31.15 ± 2.13

Zone of inhibition measure in millimeter, SD; Standard Deviation, Fluco; Fluconazole, nt; means not tested compounds.

**Table 5: Antifungal activity as percentage inhibition of the synthetic compounds (3i-xii).**

Compd.	<i>C. albicans</i> (MTCC-3617)		<i>A. niger</i> (MTCC-281)		<i>A. flavus</i> (MTCC 418)	
	50 µg/mL ± SD	100 µg/mL ± SD	50 µg/mL ± SD	100 µg/mL ± SD	50 µg/mL ± SD	100 µg/mL ± SD
3i	55.31 ± 2.48	55.27 ± 2.63	53.42 ± 1.48	56.21 ± 2.91	43.42 ± 2.48	58.21 ± 3.93
3ii	54.21 ± 1.23	58.37 ± 2.61	63.02 ± 2.02	66.19 ± 3.79	57.01 ± 3.02	60.13 ± 1.61
3iii	40.12 ± 3.13	41.82 ± 1.62	47.84 ± 1.12	41.11 ± 1.88	nt	nt

3iv	55.01 ± 2.07	59.04 ± 2.30	61.01 ± 4.59	63.21 ± 1.61	69.01 ± 1.51	72.33 ± 2.62
3v	nt	nt	61.30 ± 3.96	40.29 ± 3.31	65.65 ± 2.91	57.29 ± 5.33
3vi	47.94 ± 1.11	46.16 ± 3.81	50.61 ± 4.18	41.18 ± 4.44	47.61 ± 7.11	45.15 ± 1.41
3vii	48.41 ± 4.25	50.31 ± 1.68	41.23 ± 2.14	50.71 ± 2.36	51.21 ± 2.12	56.71 ± 2.35
3viii	57.19 ± 3.14	63.45 ± 2.80	59.67 ± 5.18	62.23 ± 2.41	60.31 ± 7.18	63.19 ± 2.44
3ix	53.19 ± 1.17	57.19 ± 1.67	49.22 ± 2.11	52.71 ± 1.31	54.29 ± 4.11	58.71 ± 2.36
3x	59.23 ± 2.41	61.27 ± 1.63	65.41 ± 1.41	51.29 ± 3.32	61.23 ± 3.17	63.71 ± 1.31
3xi	67.09 ± 4.01	64.52 ± 4.30	60.13 ± 5.59	56.12 ± 1.69	nt	nt
3xii	nt	nt	45.22 ± 2.11	48.71 ± 1.31	42.29 ± 4.11	51.71 ± 2.36
Fluco.	100.00 ± 2.35	100.00 ± 2.12	100.00 ± 2.34	100.00 ± 3.43	100.00 ± 2.34	100.00 ± 3.43

Zone of inhibition represented in percentage inhibition, SD; Standard deviation, Fluco; Fluconazole, nt; means not tested compounds.

## Conclusion

A number of compounds 3i-xii [4-(biphenyl-4-yl)-2-(substituted phenyl)-1H-imidazole] have been successfully synthesized. The pharmacological study was performed to evaluate the effects of substituent on the antibacterial and antifungal activities. The biological activity result revealed that all the newly synthetic compounds 3i-xii [4-(biphenyl-4-yl)-2-(substituted phenyl)-1H-imidazole] exhibited better antibacterial activity as compared to antifungal activity in compare to reference drug. The results of anti-bacterial screening further revealed that among all the compounds, the compound (3iv) and (3x) were observed significant anti-bacterial activity against *E. coli*, *B. subtilis* and *K. pneumoniae* while compounds (3ii), (3viii) and (3ix) as well as compounds (3xi) and (3vii) showed moderate anti-bacterial activity in compare to standard drug ciprofloxacin. The results of anti-fungal screening showed that the compound (3ii) and (3viii) showed good anti-fungal activity against *A. niger* and *A. flavus* and compound (3xi) showed notable activity against *C. albicans*. The compound (3vii) and (3ix) were shown moderate activity against *C. albicans* and *A. niger*.

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**Conflict of interest:** We declare that we have no conflict of interest.

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